EXHIBIT 5

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)
v.
Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495,
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina Theodora van Deutekom, Johannes Theodorus den Dunnen and Annemieke Aartsma-Rus).

University of Western Australia,
Junior Party
(Patents 7,960,541 and 7,807,816,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)
v.
Academisch Ziekenhuis Leiden,
Senior Party
(Application 13/550,210,
Inventor: Judith Christina Theodora van Deutekom).

University of Western Australia,
Junior Party
(Patent 8,486,907,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)
v.
Academisch Ziekenhuis Leiden,
Senior Party
(Application 14/198,992,
Inventor: Judith Christina Theodora van Deutekom).

Patent Interference Nos. 106,007, 106,008, 106,113 (RES)
(Technology Center 1600)

DECLARATION OF MATTHEW J. A. WOOD, M.D., D. PHIL.

UWA EXHIBIT 2081
University of Western Australia
v.
Academisch Ziekenhuis Leiden
Interference Nos. 106,007, 106,008 & 106,013

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I, Matthew J. A. Wood, have personal knowledge of the facts stated herein and, if called as a witness, would competently testify to the following:

I. QUALIFICATIONS

1. I am a Professor of Neuroscience at the University of Oxford in the United Kingdom. I am also a Fellow and Tutor in Medicine and Physiology at Somerville College, one of the colleges of the University of Oxford.

2. I graduated in Medicine from the University of Cape Town in 1987, working in clinical neuroscience, before gaining a doctorate in physiological sciences from the University of Oxford in 1993.

3. From 1994-1998, I was a University Lecturer in Anatomical Science in the Department of Human Anatomy and Genetics at the University of Oxford. From 1999-2010, I was a University Lecturer in Biomedical Science in the Department of Physiology, Anatomy, and Genetics at the University of Oxford.

4. Since 2013, I have been the Associate Head of the Medical Sciences Division at the University of Oxford.

5. I am a member of the British Neuroscience Association, the British Society for Gene Therapy, the U.S. Society for Neuroscience, and the American Society for Gene Therapy.

6. In 2001, I received the Young Investigator Award of the International Brain Research Organization. In 2009, I became the Vice Chair of the Scientific Advisory Board for Action Duchenne, a U.K. organization focused on developing treatments for Duchenne Muscular Dystrophy ("DMD").

7. My laboratory researches gene therapies for degenerative disorders of the nervous system and muscle, including in particular DMD. The main focus of our research is the investigation of novel therapeutic approaches using short nucleic acids that target RNA and in

particular the development of novel delivery methodologies to enhance the efficacy of therapeutic nucleic acids including antisense oligonucleotide agents for DMD. Such methodologies include the development of peptide-based and nanotechnology-based delivery agents.

8. In 2004, I joined a UK consortium of investigators studying treatment of DMD using a technique called exon skipping. This consortium, known as MDEX, is a translational medicine consortium, now comprising researchers from the UK and France, whose objective is the development of oligonucleotide based exon skipping therapies for DMD. I have since 2009 been Co-PI of this consortium, and lead a number of major DMD focused research programmes within the consortium. In 2013 I was elected to the Executive Board of TREAT NMD, originally a European Network but now a global network, whose major goal is bringing together leading neuromuscular disease specialists, patient groups and industry representatives to ensure preparedness for the trials and evaluating the neuromuscular therapies of the future while promoting best practice today.

9. To date, I have published more than 160 peer reviewed publications, including over 45 papers relating to treatments for DMD. From 2011-2014, I have published more than 70 peer-reviewed papers, including 27 directed to understanding and treating DMD.

10. I have also published numerous papers related to exon skipping therapies, the specific technology at issue in these three interferences identified in the caption above. For example, I am senior author in a submission currently under review in the journal Nature relating to restoration of the dystrophin protein by exon skipping therapy. I also have significant hands-on experience with different types of chemistries commonly used for exon skipping oligonucleotides, again including those at issue in these interferences. My additional

professional activities and experiences are set forth in my curriculum vitae, a copy of which is identified as Exh. 2003.

II. OVERVIEW OF ISSUES CONSIDERED

11. I have been asked to give my opinions on the following issues:

- whether AZL's U.S. Application No. 11/233,495 ("the '495 application"; Exh. 2041) provides a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the '495 application that the AZL applicants had possession of the full scope of claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103;
- whether the '495 application provides sufficient information to permit a person of ordinary skill in the art as of the application's filing date to practice the full scope of claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103 without undue experimentation;
- whether AZL's U.S. Application No. 13/550,210 ("the '210 application"; Exh. 2043) provides a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the '210 application that the AZL applicants had possession of the full scope of claims 11, 12, 14, 15, and 17-29;
- whether the '210 application provides sufficient information to permit a person of ordinary skill in the art as of the application's filing date to practice the full scope of claims 11, 12, 14, 15, and 17-29 without undue experimentation;

- whether AZL's U.S. Application No. 14/198,992 ("the '992 application"; Exh. 2052) provides a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the '992 application that the AZL applicants had possession of the full scope of claims 1-7 and 10-27;
- whether the '992 application provides sufficient information to permit a person of ordinary skill in the art as of the application's filing date to practice the full scope of claims 1-7 and 10-27 without undue experimentation;
- whether AZL's U.S. Application No. 14/248,279 ("the '279 application"; Exh. 2035) provides a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the '279 application that the AZL applicants had possession of the full scope of claims 1-16 and 20-26;
- whether the '279 application provides sufficient information to permit a person of ordinary skill in the art as of the application's filing date to practice the full scope of claims 1-16 and 20-26 without undue experimentation;
- whether the claims of the '495, '210, '992, and '279 applications, when read in the context of the AZL applications and the record of the examination of the patent application by the Patent Office, inform those of ordinary skill in the art with reasonable certainty about the scope of the invention recited in the claims; and

- whether before October 5, 2011, the material limitations of the '210 application claims were included in any claim presented in AZL's U.S. Application No. 12/976,381 ("the '381 application"), U.S. Application No. 12/198,007 ("the '007 application"), or the '495 application.

III. MATERIALS CONSIDERED

12. A list of the materials I have considered in preparing this declaration is attached as Appendix A.

IV. TECHNICAL BACKGROUND

A. Duchenne Muscular Dystrophy

13. DMD is an X-chromosome-linked neuromuscular genetic disease that occurs in one in every 3,500 boys born worldwide. It primarily affects male children, with most boys diagnosed between the ages of 3 to 5 years.

14. Symptoms of DMD usually appear in infants and toddlers. Affected children may experience developmental delays such as difficulty in walking, climbing stairs or standing from a sitting position. As the disease progresses, muscle weakness in the lower limbs spreads to the arms, neck and other areas. Most patients require full-time use of a wheelchair in their early teens, and then progressively lose the ability to independently perform activities of daily living such as using the restroom, bathing and feeding.

15. Upon further progression of the disease, patients experience increased difficulty in breathing due to respiratory muscle dysfunction and typically require ventilation support. Additionally, cardiac dysfunction can lead to heart failure. DMD is universally fatal, with patients usually succumbing to the disease in their twenties.

16. DMD is caused by a change or mutation in the gene that encodes a protein called dystrophin. These mutations may include large deletions (about 60-70 percent), large

duplications (about 10 percent) or other small changes (about 15-30 percent), but invariably they prevent synthesis of fully functional dystrophin protein.

17. Dystrophin plays a key structural role in muscle fiber function. In healthy muscle, dystrophin interacts with other proteins at the cell membrane to stabilize and protect the cell during regular activity involving muscle contraction and relaxation.

http://www.sarepta.com/community/disease-resources

18. Patients with DMD produce little or no dystrophin in their muscle. Without dystrophin, normal activity causes excessive damage to muscle cells, and they are ultimately replaced by fibrotic tissue and fat, leading to a progressive loss of function.

19. Despite a great medical need for a cure, as of this date there are no FDA approved therapies for treating DMD.

B. Becker Muscular Dystrophy

20. Becker Muscular Dystrophy ("BMD") also results from mutations in the dystrophin gene, but symptoms in patients with BMD are milder and display a later, and much slower, rate of progression. BMD symptoms are variable but include slowly progressing muscle weakness, with the ability to walk typically continuing well into adulthood.

21. Patients with BMD generally carry a mutation (or several) that causes the body to make a functional, though shorter, form of the dystrophin protein. (Exh. 2004 at 524.) Many BMD patients make dystrophin protein missing portions, even substantial portions, of the central domain of the dystrophin protein. This means that loss of even a substantial part of the central domain of the dystrophin protein can occur with relatively little impact on protein function. (Exh. 2005 at 172.)

22. This contrasts with mutations causing DMD, which typically disrupt reading-frame or prevent synthesis of either end of the dystrophin protein. (Exh. 2004 at 524.)

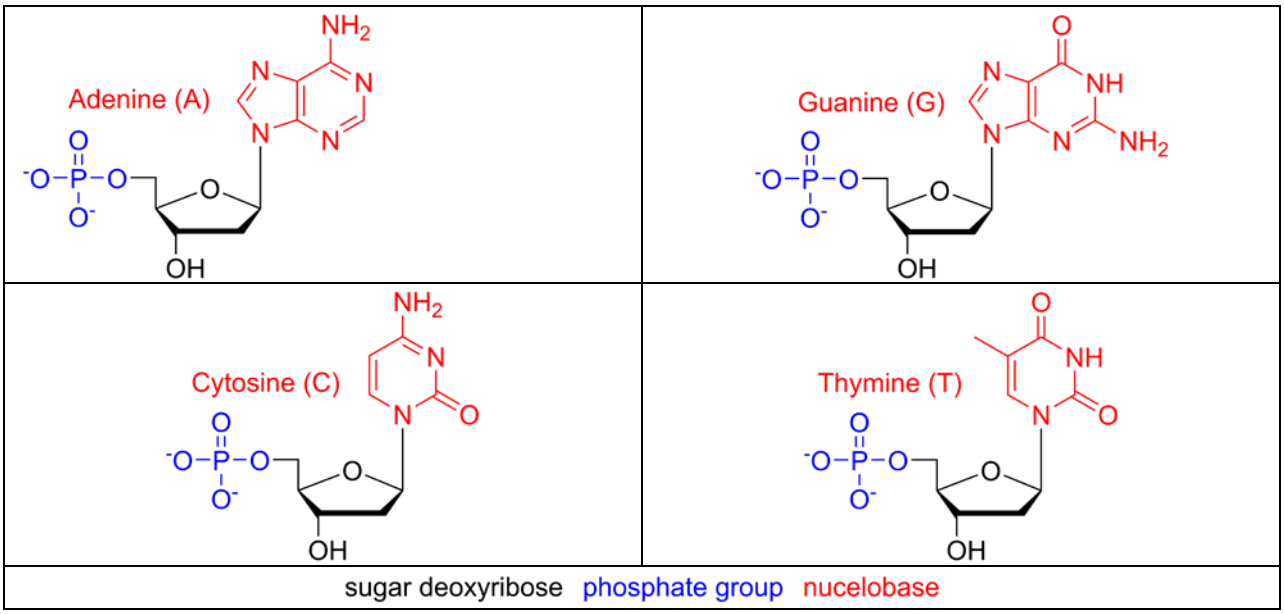
23. The goal of exon skipping therapies to treat DMD, the technology at issue in these proceedings, is to correct for specific genetic mutations that cause DMD and restore the patient's ability to make a functional, though shorter, form of the dystrophin protein, similar to dystrophin protein found in BMD patients. To understand how this works, some additional background is required.

C. Transcription, Splicing, and Translation

24. Mammalian cells are surrounded by a membrane and usually contain an inner body, the nucleus, which is also surrounded by a membrane. Deoxyribonucleic acid ("DNA"), found in the nucleus of cells, carries the genetic information used in the development and functioning of all living organisms.

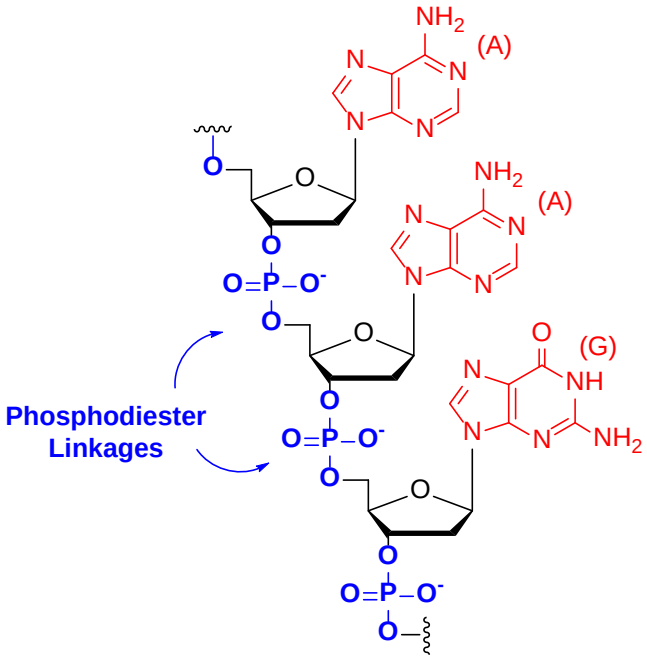
25. DNA is constructed from four main nucleotide building blocks. Each of these nucleotides contains a phosphate group linked to a five-carbon-atom deoxyribose sugar group, which in turn is joined to one of four possible nucleobases: adenine (A), cytosine (C), guanine (G), and thymine (T).

26. The figure below shows each of the four naturally occurring nucleotides of DNA, all of which contain the sugar deoxyribose, a phosphate group, and a nucleobase.



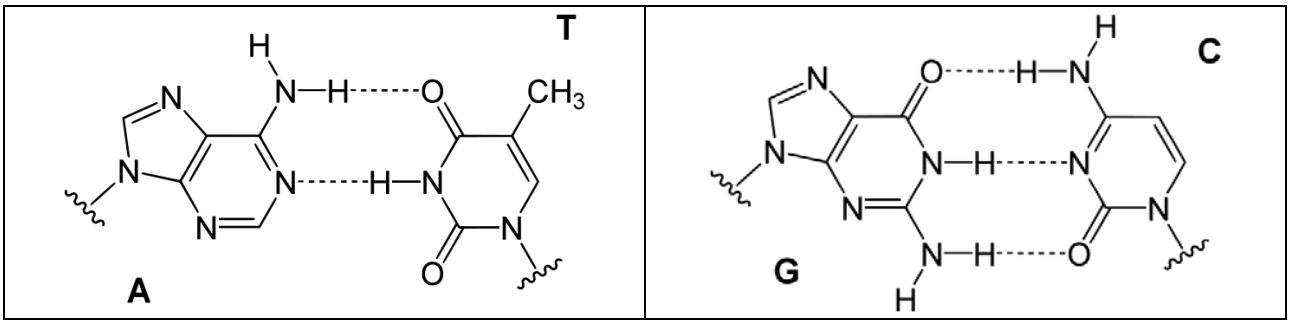
27. The nucleobases "adenine" and "guanine" are examples of purines, which are bicyclic aromatic compounds. The nucleobases "cytosine" and "thymine" are examples of pyrimidines, which are monocyclic aromatic compounds.

28. Nucleotides in DNA are joined together by internucleotide linkages between the sugar of one nucleotide and the phosphate of the next. These bonds are called phosphodiester linkages. The following figure shows a portion of a DNA polynucleotide chain, including the phosphodiester linkages that connect the nucleotides.



As can be seen above, each nucleotide in the chain contains a nucleobase and a sugar, sometimes called the chemical backbone, and each nucleotide is connected by the internucleotide linkage.

29. The four naturally occurring DNA nucleobases form "complementary" pairs that interact through hydrogen bonds, with the purines interacting with the pyrimidines. Adenine (A) interacts with thymine (T), and cytosine (C) interacts with guanine (G). This is called Watson-Crick base pairing and is illustrated in the following figure for A-T and G-C pairing, with dotted lines representing hydrogen bonds:

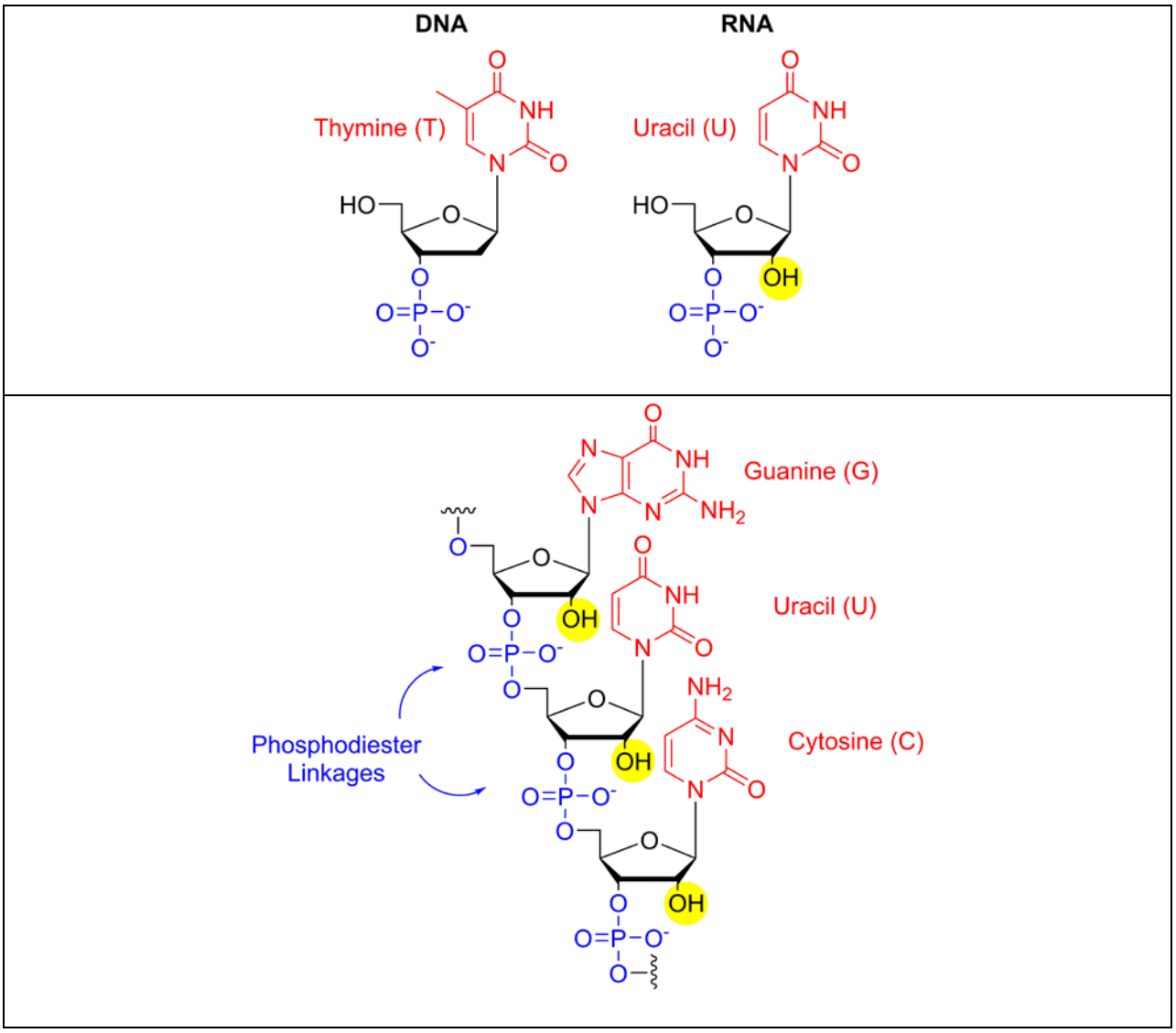


30. Base pairing allows two complementary DNA strands to form a double helix. The complementary nature of base pairing also allows cells to make copies of DNA strands, because the sequence of nucleobases on one strand dictates the nucleobase sequence of the other strand.

31. In cells, DNA is organized into very long structures called chromosomes. Human chromosomes contain about 22,000 genes, each of which encodes a different protein. Despite this, substantial portions of our chromosomes do not encode proteins. It is estimated that about 1.5% of the human genome consists of protein-coding regions, with the remainder consisting of non-coding sequences.

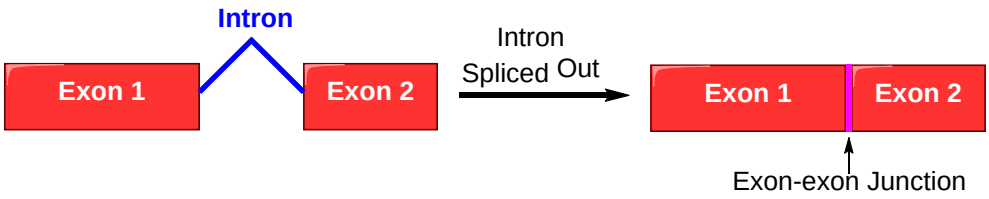
32. To create proteins, DNA in the nucleus needs to be "transcribed" into messenger ribonucleic acid ("mRNA").

33. Like DNA, RNA is constructed from four nucleotide building blocks. Each RNA nucleotide contains a phosphate group linked to a ribose sugar group, which in turn is linked to one of four possible nucleobases: adenine (A), cytosine (C), guanine (G), or uracil (U). Naturally occurring RNA therefore chemically differs from DNA in that (1) the sugar group is ribose instead of deoxyribose and (2) RNA contains the pyrimidine nucleobase uracil (U) instead of the nucleobase thymine (T). The following figure shows a portion of an RNA polynucleotide chain, including the phosphodiester linkages that connect each ribonucleotide. As can be seen below, each nucleotide in the RNA chain contains a nucleobase and a ribose sugar, and each nucleotide is connected by an internucleotide linkage.



34. Transcription of DNA into mRNA is a multi-step process. In the nucleus, genes are transcribed to form a precursor mRNA (or "pre-mRNA"), with the nucleobase sequence of the DNA dictating the nucleobase sequence of the pre-mRNA. These nuclear pre-mRNAs include "exons," segments that encode protein that are retained in the mature mRNA, as well as "introns," which are removed from the pre-mRNA in a process called "splicing." Splicing of the pre-mRNA transcript occurs in the nucleus shortly after transcription, and is mediated by a large complex of proteins and RNAs called the "spliceosome."

35. A schematic of two exons separated by a single intron is shown in the following figure. During the splicing process, the intron (or "intervening sequence") is removed (spliced) from the mature mRNA.



36. Introns contain a donor site at one end and an acceptor site at the other. Both the donor and acceptor sites are required for splicing. Certain other nucleotide sequences, called intronic or exonic splicing enhancers or intronic/exonic splicing silencers, also can influence splicing efficiency.

37. Exon skipping, the subject of the technology at issue in these interferences, involves the experimental manipulation of splicing events. As explained in the following section, exon skipping aims to manipulate pre-mRNA splicing using antisense oligonucleotides ("AONs").

38. Following pre-mRNA splicing, the "mature" mRNA is transported out of the nucleus. That mRNA can then be "translated" into protein.

39. It is useful to consider the example of dystrophin in considering these concepts. The dystrophin gene is one of the longest human genes, covering about 2,500,000 nucleotides of the X chromosome. In a healthy individual, the transcription machinery in the nucleus produces full-length dystrophin pre-mRNA transcripts measuring about 2,400,000 nucleotides. These full-length pre-mRNA transcripts contain 79 exons and 78 introns.

40. The splicing machinery in the nucleus then removes all 78 introns, many of which are very large, creating a mature transcript of about 14,000 nucleotides. It is the splicing

machinery that therefore generates the actual coding region for the protein by splicing together the exons from the pre-mRNA.[1]

41. As mentioned, after splicing the dystrophin mRNA is transferred out of the nucleus into the cytoplasm, where the dystrophin protein is produced.

D. Conceptual Framework for Treating DMD by Exon Skipping

42. As discussed above, loss of a portion of the dystrophin protein, even a substantial portion of the dystrophin protein, can occur with relatively little impact on protein function.

43. However, in many patients with DMD, deletion of an exon or exons produce a "frame shift" such that the remaining exons are misaligned or "out of frame," interrupting proper translation of the genetic code into protein. Patients with these mutations typically produce little or no functional dystrophin protein.

44. Exon skipping seeks to realign the remaining exons, making them "in-frame," by causing the cellular machinery to "skip" over an exon in the pre-mRNA. By restoring the reading frame, the cellular machinery is able to translate the RNA into a functional, though shorter, form of dystrophin.

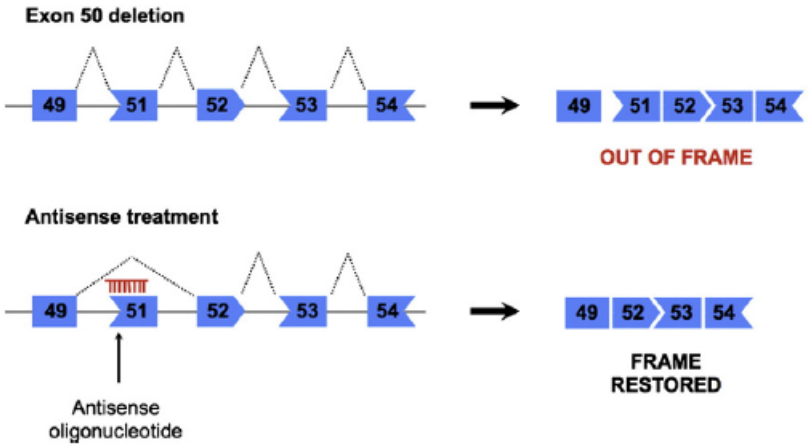
45. Exon skipping therapies therefore must be patient specific, in that patients with different mutations need to be treated with different reagents that skip different exons. With respect to patients with DMD, while deletions are spread across the 79 DMD exons, there are

[1] Healthy patients produce at least seven shorter forms of dystrophin protein, each transcribed using an alternative promoter. There are also likely to be considerably more forms of dystrophin owing to the presence of multiple alternative splicing events. Nevertheless, the full-length skeletal muscle isoform encodes a protein that is 3685 amino acids in length. (Exh. 2005 at 170.)

specific "hotspot" regions where deletions are particularly common, such as between exons 45 and 55 where around 70% of deletions are located. (Exh. 2005 at 172.) Patients carrying these mutations are promising candidates for exon therapy treatments.

46. Other patients with DMD carry "nonsense" mutations that cause premature termination of the dystrophin protein. Nonsense mutations are point mutations that introduce a premature "stop" codon, preventing translation of full-length protein. These patients also typically produce little or no functional dystrophin protein. Nonsense mutations are believed to account for around 15% of known DMD mutations. Exon skipping therapies could also be designed to skip exons containing these nonsense mutations, such that cells would make functional, though shorter, dystrophin protein. Of course, in these cases the reading frame must still be maintained, so single exon skipping for these mutations is limited to those exons that are not frame-shifted. However, this would still apply to around 47% of patients with dystrophin nonsense mutations. (Exh. 2005 at 172.)

47. The following figure shows the principle of exon skipping in DMD. In this example, exon 50 of DMD is deleted, causing a frameshift in the resulting spliced mRNA. Addition of an AON (shown in red and annotated with an arrow) that specifically binds to a target sequence within exon 51 mediates skipping of this additional exon by the spliceosome (the cellular machinery responsible for exon skipping), such that exon 49 is spliced directly to exon 52. Although the resulting mRNA is missing the portion of the dystrophin protein encoded by exons 50 and 51, this has a minimal effect on overall protein function.



(Exh. 2005 at 173.)

48. Available data suggests that up to approximately 80% of DMD patients carry mutations potentially amenable to exon skipping. Studies show that approximately 13% of DMD patients are candidates for treatment by exon 51 skipping, and another 8% of patients are candidates for treatment by exon 53 skipping. (Exh. 2005 at 172.)

E. Antisense Oligonucleotides for Exon Skipping

1. Requirements for exon skipping

49. AONs are the primary therapeutics being investigated for exon skipping. AONs are single-stranded, short lengths of nucleotides. AONs have molecular weights 10-20 times that of a small molecule and, as explained below, are subject to a multitude of possible chemical modifications.

50. To be effective therapeutic agents for modulating splicing, AONs ideally possess a number of intrinsic properties.

- First, the AON in question should bind in a sequence-specific manner to the target pre-mRNA: the higher the specificity, the less chance of unwanted off-target effects.

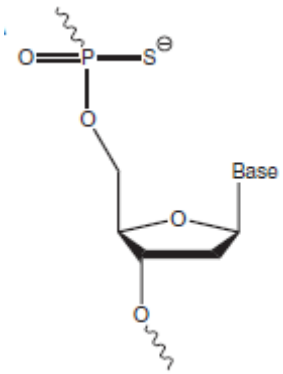
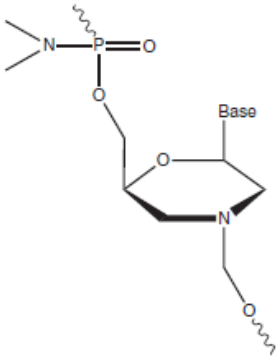
- Second, the AON needs to bind to its target with appropriate affinity. If the AON binds poorly, it will not induce exon skipping (or will not induce sufficient exon skipping). On the other hand, if the AON binds too tightly, it will not detach quickly enough (or at all) from a particular target transcript. Detachment is essential because dystrophin pre-mRNAs are constantly being generated in muscle cells. If detachment is too slow (or does not occur), the AON will not induce sufficient exon skipping.
- Third, the AON needs to be delivered effectively to the appropriate tissue type upon administration.
- Fourth, upon reaching the appropriate tissue type, the AON needs to penetrate into the cell and also into the appropriate intracellular compartment. Because pre-mRNA splicing takes place in the nucleus, it is critical that an exon skipping AON localize to the nucleus once it is taken up.
- Fifth, because the body contains numerous proteins that degrade oligonucleotides (called "nucleases"), an exon skipping AON should be resistant to nuclease degradation to allow it to reach its desired target intact and to maximize its potential duration of action once there.
- Sixth, once complexed with the target pre-mRNA, the AON/RNA duplex should be resistant to the nuclease RNase H, which normally degrades RNA bound up in duplexes.
- Seventh, the AON should not be toxic.
- Eighth, the AON should have favorable pharmacokinetic and pharmacodynamic properties.

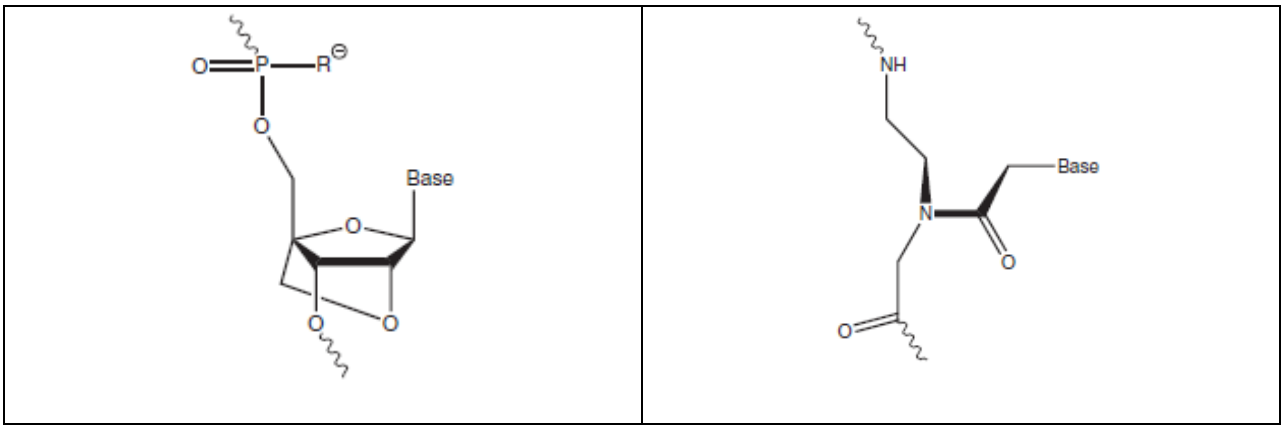
(Exh. 2005 at 173.)

2. Prominent classes of AON proposed for exon skipping

51. Because chemists can make changes at almost every position of the nucleobase, chemical backbone, and internucleotide linkages, the number of possible modifications to naturally occurring AONs is immense. In an effort to cope with the many requirements for exon skipping, scientists have explored many different AON chemistries, including AONs with modifications to the nucleobase, the backbone, the internucleotide linkages, and combinations of each.

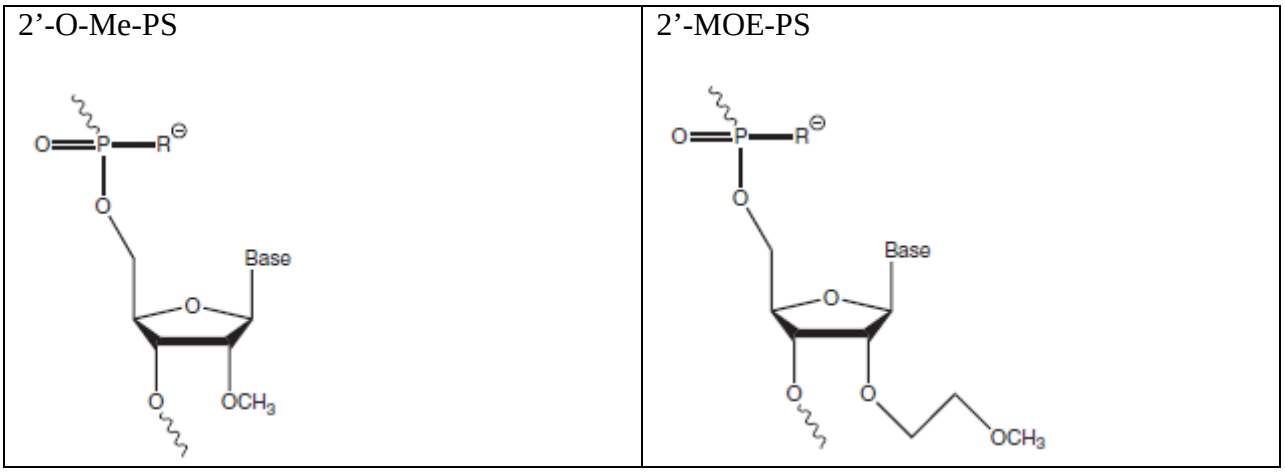
52. AON chemistries can vary significantly from naturally occurring nucleotides. However, they preserve the ability to form Watson-Crick base pairs with pre-mRNA through the maintenance of nucleobases (sometimes modified) in the correct spatial conformation. Although not exhaustive, a selection of significant types of AON chemistries proposed for exon skipping is illustrated in the following figure and discussed below. These include phosphorothioates ("PS"), morpholinos ("PMOs"), locked nucleic acids ("LNAs"), and peptide nucleic acids ("PNAs").

Phosphorothioate (PS) 	Morpholino (PMO) 
Locked Nucleic Acid (LNA)	Peptide Nucleic Acid (PNA)



(Exh. 2061 at 38.)

53. Phosphorothioates are chemically similar to RNA, but the non-bridging oxygen atom of the phosphate group of RNA is replaced by a sulfur atom. As illustrated in the following figure, commonly used phosphorothioates include 2'-O-methyl phosphorothioate ("2'-O-Me-PS"), which have a methyl group attached to the oxygen atom at the 2' position of the ribose ring, as well as 2'-O-methoxyethyl phosphorothioate ("2'-MOE-PS"), which add a methoxy group instead of a methyl group. These modifications confer some nuclease resistance.



(Exh. 2061 at 38.)

54. Phosphorothioates retain a negative charge. As explained below, this property aids in their solubility, but it also makes them "sticky," meaning that they have a tendency to

nonspecifically bind proteins, which can prove problematic for efficient delivery *in vivo* and lead to toxicity.

55. Phosphorodiamidate morpholino oligomers (called "morpholinos" or "PMOs") have six-membered morpholine rings in place of ribose. Additionally, each "nucleotide" is joined together by phosphorodiamidate linkages rather than phosphodiester linkages.

56. Morpholinos are nuclease and RNase H resistant and have no charge on their backbone at physiologic pH. Morpholinos are not toxic and are very stable, as the majority of administered compound is excreted essentially unchanged in urine. Unlike phosphorothioates, they have no net electrical charge and therefore do not tend to interact with non-target molecules. (Exh. 2005 at 174.)

57. Peptide nucleic acids ("PNAs") replace the sugar group of DNA and RNA with repeating N-(2-aminoethyl)-glycine units linked by peptide bonds (which are typically found in proteins, not nucleic acids).

58. Like morpholinos, PNAs are uncharged at physiologic pH. PNAs are also resistant to enzyme degradation. PNAs tend to have very high target binding affinity, but PNA/RNA mismatches are more destabilizing than a similar mismatch in an RNA/RNA duplex. Unmodified PNAs cannot readily cross cell membranes, and PNAs are less soluble than RNA oligonucleotides. (Exh. 2006 at 4508.)

59. As compared to RNA, locked nucleic acids ("LNAs") contain a bond connecting the 2'-oxygen of the ribose with the 4'-carbon. This bond "locks" the sugar portion of the nucleotide in a particular confirmation, and as a consequence LNAs are conformationally inflexible. (Exh. 2009 at 1.)

60. LNAs have an extremely high affinity for RNA and DNA. Additionally, LNAs are considered non-toxic and are RNase H resistant. However, full-length LNAs generate an effect mainly in liver, colon, and small intestine after systemic delivery, and therefore there may be issues with delivery to muscle.

61. Many modifications have been and can be made within these commonly used frameworks. For example, non-natural modified nucleobases could be used in place of A, C, G, T, and U. Such well-known nucleobases include, by way of example only, 5-substituted pyrimidines; 6-aza-pyrimidines; and N-2, N-6, and O-6 substituted purines.

62. Such non-natural nucleobases may bind more or less tightly than their natural equivalent, and therefore may alter the affinity of a particular AON for its target. For example, 5-methyl-cytosine increases duplex stability as compared to unmodified cytosine (C). (Exh. 2007 at 3613.)

63. Researchers have also investigated AONs made with internucleotide linkages other than those called out above. These include, by way of example only, phosphotriester, methylphosphonate, phosphoroamidate, carbonyl, and sulfonyl linkages. (Exh. 2008 at 189.) Changing these internucleotide linkages can alter binding specificity and affinity, nuclease resistance, delivery to target tissue, uptake into cells, and intracellular targeting.

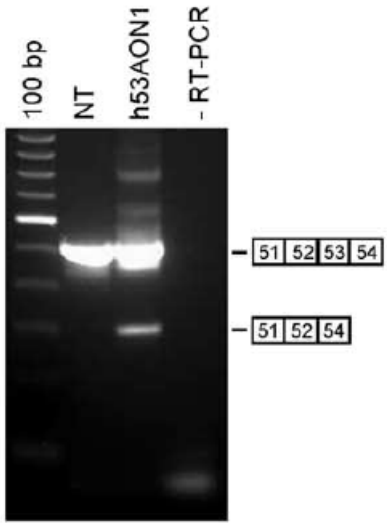
64. AONs can also be made that are synthesized partly with one chemistry and partly from another. These are called “chimeric” or “hybrid” AONs. For example, “gapmers” have been studied that contain a central region of 2’-O-Me-PS nucleotides flanked by LNAs. (Exh. 2006 at 4509.) Similarly, LNA/2’-O-Me RNA chimeras have been developed to improve the potency and specificity of their action. (Exh. 2006 at 4509.)

3. *In vitro* skipping assays

65. Exon skipping is typically studied in cultured cells. Some studies use primary human myoblasts (muscle cells) isolated from human muscle biopsies of affected or non-affected individuals. Other studies use human muscle tumor cell lines.

66. Regardless of the cell source, the cultured cells are often "transfected" with relatively high concentrations of AONs, often ranging from 100 nM to 1 mM. To facilitate cell transfection, chemical reagents such as polyethylenimine ("PEI") or lipofectamine are added to the cell cultures to help the AON penetrate the cellular membrane. These agents are relatively toxic and consequently are not suitable for use in patients. Alternatively, cell cultures can be transfected by nucleofection, which uses electricity to enable the AONs to directly enter the nucleus of target cells. Although these transfection techniques can be used *in vitro*, they cannot for safety reasons be used for delivering drug to patients.

67. Although different methods can be used to monitor exon skipping *in vitro*, the primary method is called RT-PCR. In this technique, RNA is isolated from cultured cells following transfection with the AON. An oligonucleotide adjacent to the target exon is used to "prime" the enzyme reverse transcriptase ("RT"), which converts the RNA into a complementary DNA (cDNA). That cDNA is then used as a template for exponential amplification using the polymerase chain reaction ("PCR"). If the AON induces exon skipping, the PCR product will be shorter than it otherwise would. This is depicted in the following figure, which shows that the AON induces formation of a smaller band having faster mobility than the control sample:



(Adapted from Exh. 2010, Fig. 1(i).) In this example, exon skipping appears relatively inefficient, as the presence of the large upper band reveals that most of the product contains exon 53. Notably, RT-PCR provides no information as to whether or not dystrophin protein is produced. In the case of DMD, it is the protein, not the RNA, that is necessary to restore muscle function.

F. *In Vitro* Exon Skipping Experiments Are Unpredictable

68. Even in these relatively controlled *in vitro* skipping studies, exon skipping is unpredictable.

69. As stated by the AZL group in a 2001 publication, "[t]he efficacy of AONs is largely determined by their binding affinity for the target sequence. Due to base composition and pre-mRNA secondary or tertiary structure, ***it is difficult to predict which AONs are capable of binding the target sequence***." (Exh. 2012 at 1548; emphasis added.)

70. Similarly, in 2002, the AZL group concluded as follows: "We therefore ***have no insight*** into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus ***the effectivity of any designed AON, will therefore still***

have to be tested empirically in the cells, as was done in this study." (Exh. 2010 at S76; emphasis added.)

71. A 2007 paper co-authored by several members of the AZL group states that "several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], ***there are still no clear rules to guide investigators in their design***, and in mouse and human muscle cells *in vitro* ***there is great variability for different targets and exons***." (Exh. 2013 at 807; emphasis added.)

72. In 2009, the AZL group wrote that while existing software programs can facilitate exon skipping AON design, "in general ***a trial and error procedure*** is still involved to identify potent AONs." (Exh. 2014 at 548; emphasis added.)

73. There are numerous examples of this *in vitro* unpredictability. For example, the AZL group reported in 2001 that mAON9 induced exon skipping in cultured mouse muscle cells, but mAON8 did not. These AONs were both made with the same 2'-O-Me-PS chemistry and both apparently bound to their target sequences. Moreover, these AONs substantially overlapped, as both contained the nucleobase sequence "UUAGCUGCUGC" as well as additional nucleobases complementary to the mouse dystrophin gene. Yet one induced skipping of exon 46, and the other did not. (Exh. 2012 at 1548.)

74. Another example was published by Wu and coworkers in 2011. These researchers screened a series of AONs covering more than two thirds of human dystrophin exon 50 and two flanking intron sequences. A subset of the tested sequences, all made with 2'-O-Me-PS chemistry, is shown in the Table below:

Name	Target[2]	2'-O-Me-PS AON Sequence	Length	Effect
AO3PS	-19+1	UCUUUAACAGAAAAGCAUAC	20	-
AO4PS	-19+3	CCUCUUUAACAGAAAAGCAUAC	22	4%
AO5PS	-19+8	AACUUCCUCUUUAACAGAAAAGCAUAC	27	21%
AO6PS	-19+13	CUUCUAACUUCCUCUUUAACAGAAAAGCAUAC	32	3%

(Exh. 2015 at 4.) The 20-mer AO3PS induced no detectable exon skipping. The 22-mer AO4PS, differing only in having two additional nucleotides complementary to the *DMD* gene, induced detectable exon skipping in 4% of cells. Adding an additional five nucleotides increased exon skipping to 21%. However, adding five more nucleotides largely abrogated this effect. Consistent with this, the AZL group noted in a 2009 publication that increasing AON length could decrease exon skipping efficiency. (Exh. 2014 at 552.) The observations on AON length versus skipping efficiency reported by Wu *et al.* are consistent with my experience. AONs have an optimal length, which is a result of a number of factors including nucleotide sequence, chemical modifications, and target accessibility, and when that length is either not reached or is exceeded the skipping efficiency drops off. Consequently, I would expect that the great majority of longer AONs, on the order of 50 nucleotides or longer, will not efficiently induce skipping for a number of reasons, if they induce it at all, to be useful as therapeutic agents for treating DMD. Those reasons include access to the complementary sequence in the pre-mRNA, binding affinity of the AON for the complementary sequence, and the ability to transfect longer AONs into cells.

75. Heemskerk and coworkers, another publication from the AZL group, also highlights this unpredictability. (Exh. 2020 at 259-60.) For example, Heemskerk analyzed exon skipping by RT-PCR of mouse exon 23 with a "short" 2'-O-Me-PS AON that was 20 nucleotides

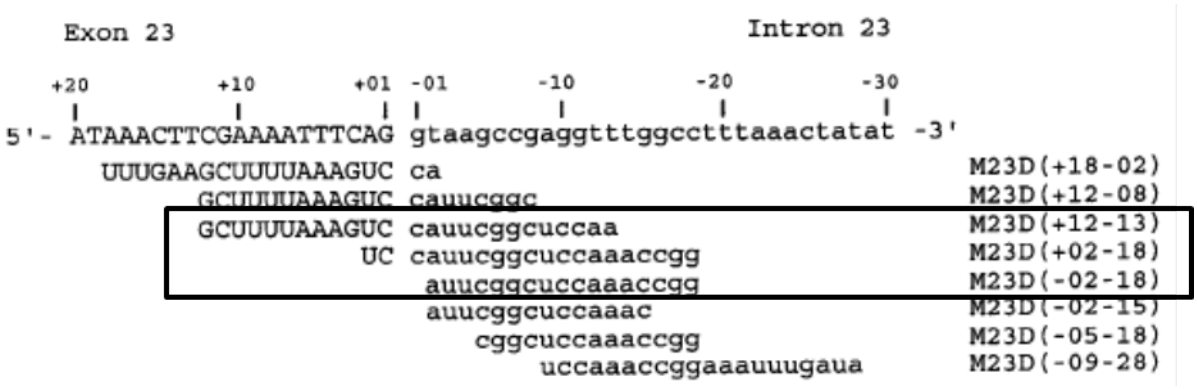
[2] The Target column shows the coordinates of the target site relative to the pre-mRNA sequence. "+" represents an exonic position and "-" represents an intronic position, with the numbers representing the first and last nucleotides AON target sequence. (Exh. 2015 at 4.)

in length, a "long" 2'-O-Me-PS AON that was 25 nucleotides in length, and the "long" AON made as a PMO. The sequences of these AONs are shown below.

Name	AON Sequence (3' to 5')	Length
m23AON5'ss	UCCAUUCGGCUCCAAACCGG	20
m23AON5'sslong	UAAAGUCCAUUCGGCUCCAAACCGG	25
m23PMO5'ss	TAAAGTCCATTCGGCTCCAAACCGG	25

According to the authors, "[t]he PMO induces significantly higher levels of exon skipping than both [2'-O-Me-PS] AONs." (Exh. 2020 at 259.) But "[t]he long [2'-O-Me-PS] is significantly less efficient than the short version." (Exh. 2020 at 259.) This data shows the complex interactions between nucleotide length, nucleotide sequence, internucleotide linkages, and chemical backbone, and reinforces the need for empirically testing each chemically distinct AON.

76. Another study, authored by Dr. Wilton's group at UWA, examined skipping of exon 23 from the mouse DMD gene by RT-PCR following transfection with a series of overlapping 2'-Me-O-PS AONs, as shown in the following figure. Of the AONs tested, only M23D(+12-13), M23D(+02-18), and M23D(-02-18) were effective in inducing detectable exon skipping. (Exh. 2017 at 647.)



(Exh. 2017 at 646.) Notably, the shorter AON M23D(-02-18), which is only 17 nucleotides in

length, was particularly efficient at inducing skipping and was reported to induce exon skipping at concentrations as low as 5 nM. The authors concluded that they could improve "the efficiency of the technique" by "reduc[ing] the size and the effective dose of the AO[N]s" examined. (Exh. 2017 at 644.)

77. Arechavala-Gomeza and colleagues investigated eight specific AON sequences targeting human DMD exon 51 using two different chemical forms (2'-O-Me-PS and morpholino) in human muscle cells, human muscle explants, and human muscle explants from patients with DMD. (Exh. 2013 at 798.) Five AONs targeting the 5' splice site were "surprisingly" determined to be largely ineffective at inducing skipping of exon 51. (Exh. 2013 at 803.) Three other overlapping sequences complementary to potions of exon 51 were each capable of inducing exon 51 skipping in cells from healthy patients, including sequence B30 (targeting +66+95) and A20 (targeting +68+87. (Exh. 2013 at 803.) But B30 induced significantly better exon skipping in cells derived from a DMD patient with a deletion in exons 48 and 50 than A20. (Exh. 2013 at 805 ("the skip achieved with AO A20 was less efficient").) Similarly, B30 induced significantly better skipping in cells derived from a DMD patient with a deletion in exon 50 than A20. (Exh. 2013 at 805 ("the percentage of the skip was 13% for AO[N] A20 and 73% for AO[N] B30.") This shows that both nucleobase sequence and target cell type influence exon skipping.

78. Several factors complicate analysis of these and other studies. First, different AONs show varying effectiveness on different cell types (for example, cells from healthy individuals or DMD patients), as was observed in the Arechavala-Gomeza publication discussed above. Those authors report that "the very nature of this targeted exon skipping approach makes it impossible to test many of the specific sequences to be used in humans in healthy volunteers,

because of the potential for disrupting the intact dystrophin open reading frame, leading to nonfunctional dystrophins." (Exh. 2013 at 808; *see also* Exh. 2018 at 909.) Similarly, an AON that appears to have activity on one type of patient cells, such as skeletal muscle, may not have activity in other types of patient cells, such as cardiac muscle for reasons such as the ability of AONs to penetrate the respective cell types. (Exh. 2005 at 179.)

79. Second, *in vitro* exon skipping studies often use transfection reagents such as PEI that in essence form nanoparticles. It is impossible to know the actual AON dose administered to cells because these particles form suspensions. Complicating matters further, different reagents are used for transfecting cells with AONs having different chemical backbones, undermining "dose" and "efficiency" comparisons across studies. For example, we have recently shown that the *in vivo* activity of anionic AONs is correctly modeled *in vitro* only when using gymnotic delivery, that is, transfection of the AON into cells in the absence of a delivery agent like PEI. (Exh. 2011.)

80. Third, even *in vitro*, it is difficult to extrapolate results from one AON class (for example, a morpholino) to another. Because different AON chemistries influence binding affinity, each type of AON will have different binding characteristics, even with identical nucleobase sequences. This is reflected in the optimal lengths observed for AONs of different types: although there may be exceptions, in my experience, the typical length for an exon skipping 2'-O-Me-PS is 18-20 nucleotides; the typical length for a morpholino is 22-30 nucleotides; the typical length for a PNA is 22-25 nucleotides; and the typical length for an LNA is 13-18 nucleotides. Thus, if one attempted exon skipping with a morpholino AON using a nucleobase sequence that induced *in vitro* skipping when contained in a LNA AON, it would be unlikely to work. Conversely, if one attempted exon skipping with a LNA AON using a

nucleobase sequence that induced *in vitro* skipping with a morpholino AON backbone, it also would be unlikely to work, and moreover would likely bind to other parts of the genome because of the relatively high binding affinity of LNAs.

81. I am not aware of anyone testing any AONs of longer than 40 nucleotides in any exon skipping assay, regardless of AON chemistry.

G. Mismatches Unpredictably Alter Efficacy of AON Exon Skipping Activity

82. A mismatch occurs when there is a discrepancy in the Watson-Crick base pairing of the AON and the target pre-mRNA. Several studies have evaluated the effects of mismatches on exon skipping.

83. One study evaluated AONs designed against exon 19 of the mouse DMD gene in inducing skipping of the human DMD gene. With the exception of one AON containing seven mismatched bases, all mouse-specific AONs induced exon 19 skipping in human cells. However, 20- to 100-fold higher concentrations of mismatched 2'-O-Me-PS AONs were required as compared to perfectly complementary AONs. This was believed to result from the reduced annealing potential caused by the mismatched nucleobases. (Exh. 2004 at 525.)

84. Another study evaluated a panel of AONs designed to skip exon 25 from human dystrophin in normal and dystrophic patient cells. While the investigators expected that a single mismatch mutation would compromise AON binding and efficiency, the mismatched AON actually induced exon skipping *more* efficiently than a perfectly complementary AON (Exh. 2019 at 5.) As stated by the investigators, "most unexpectedly, H25A(+95+119), which annealed across the insertion and was therefore mismatched, induced the most robust exon skipping." (Exh. 2019 at 5.) In some instances, mismatches can therefore increase exon skipping efficiency.

85. Another study revealed unpredictable interactions between mismatches and AON backbone type. There, the investigators investigated skipping of mouse *DMD* exons by AONs designed against the human *DMD* gene. The authors explained:

> For the longer [2'-O-Me-PS] and PMO [morpholino] AONs, there were at least two mismatches with the mouse sequence. For the [2'-O-Me-PS], these mismatches almost completely abolished AON efficacy. By contrast, two of the four PMOs tested induced skipping of the murine exon. For exon 51, this aspecific skipping was at a lower level than that observed for human exon 51. However, for exon 45, the skipping levels of the mouse and human exons were similar.

(Exh. 2020 at 264.) Thus, some mismatches abolished AON activity, while others did not. And the effect of the mismatches in some cases depended upon the particular chemical backbone used to construct the AON. Notably, the authors warn that the chance of mistargeting "will increase significantly" if AONs are unable to discriminate between their target sequence and a sequence containing two mismatches. (Exh. 2020 at 264.)

86. Mismatches between an AON and its target sequence in the dystrophin pre-mRNA, therefore, will affect the ability of the AON to induce exon skipping, but one cannot predict *a priori* the impact any given mismatch(es) will have on exon skipping activity, whether positive or negative. This was true in March 2003 and is still true today.

H. Additional Challenges with *In Vivo* Exon Skipping

1. AONs have yet to fulfill their potential

87. No exon skipping drug has ever been approved by FDA.

88. In fact, despite more than 30 years of research, only two AON drugs have ever been approved by FDA for any purpose. The first, Vitravene, was approved in 1998 for intravitreal injection (into the eye), but is no longer marketed. Vitravene was superseded in the marketplace by small molecule protease inhibitors and combination treatments. (Exh. 2021.)

89. The other (Kynamro) likely works in part because the key cells it targets are liver cells, which are believed to be unusually susceptible to uptake of "naked" AONs without any special chemical modification or vehicle to facilitate delivery. (Exh. 2022 at 4.) The relative paucity of marketed AONs shows that the unpredictability of this technology extends across all possible therapeutic uses for these drugs, and is not limited to exon skipping. Even when a particular AON chemistry is found to be suitable for one application, it is unlikely to work for another.

2. Drug delivery as a barrier to effective treatment

90. A major barrier to obtaining effective exon skipping *in vivo* is drug delivery. For treatment of DMD, the design of the AON must allow effective delivery to skeletal muscle and cardiac muscle, and potentially other tissues. This has been, and remains, a significant technical challenge, as it requires "systemic" delivery throughout the body.

91. The drug delivery challenges associated with exon skipping have been well-documented in the scientific literature. For example, a 2001 publication states as follows:

> [L]ike all gene therapy protocols, ***the universal problem of delivery*** needs to be continually reassessed. Systemic delivery rather than intramuscular injection will undoubtedly be required to distribute the [AONs] if any significant clinical efficacy is to be obtained. Further experiments are necessary to address this problem of delivery . . .
>
> Exh. 2023 at 47; emphasis added.)

92. In 2002, the AZL group published an article in which they stated that "***theroretically***" targeted exon skipping "***may be*** therapeutically applicable." (Exh. 2010 at S71; emphasis added.) In 2003, the AZL group explained that "[o]ur results indicate that, ***provided that a suitable means of administration for the AONs is developed***, antisense-induced reading frame correction ***will be*** a promising therapeutic approach for many DMD patients carrying different deletions and point mutations." (Exh. 2018 at 911; emphasis added.)

93. In 2004, the AZL group wrote as follows:

> [I]t may be clear that following injections of reasonable (i.e. affordable) doses of pure AON without any delivery compound, the transfer of AONs into the nuclei of myofibers is too poor to allow sufficient levels of skipping. Therefore, various compounds should be evaluated to identify one that allows high delivery efficiencies without provoking significant toxic side effects. We show here that PEI, compared to the SAINT reagent, was more efficient in delivering the AONs into the myofibers and facilitating exon skipping. However, as expected from previous studies [25,26], PEI is toxic and induces extensive fiber degeneration and regeneration, with dose dependent infiltration of cytotoxic and helper T cells.

(Exh. 2024 at 238.)

94. A 2005 publication co-authored by Dr. van Ommen of the AZL group states that "[a]dditional significant development will be necessary to improve the delivery aspects of AON before the antisense approach could be regarded as a realistic therapeutic option in DMD." (Exh. 2025 at 450.)

95. A 2011 publication, discussing the use of AONs for treating cancer, states that "[d]espite huge expenditure on a vast array of delivery strategies, carrier molecules, etc., all of which suffer from cost issues, toxicity, poor delivery to tumors, or a combination, ***the foremost technologic hurdle blocking clinical progress for therapeutic [AONs]*** in cancer ***is delivery***." (Exh. 2026 at 6371; emphasis added.) These hurdles similarly exist for using AONs designed to treat DMD.

96. In 2013, I authored a review article characterizing AON drug delivery for treatment of DMD as a "significant and ever-present challenge," stating as follows:

> One of the most ***significant and ever-present challenges facing development of any new therapeutic agent is that of drug delivery***. This holds just as true for oligonucleotide-based therapies and indeed even the most efficient AON in vitro can only ever be as good as its in vivo delivery system. ***In DMD, the primary therapeutic target is skeletal muscle. This itself is no small task***, since skeletal muscle typically makes up between 30 and 40% of total body mass. Added to this, BMD patients with in-frame deletions comparable to those that would result from exon skipping treatments currently in development (e.g. exons 51, 53 and 45–55) have been found to express at least 40% of the dystrophin protein levels

> expressed by controls and so AON delivery must hope to aim for similar levels of restoration.

(Exh. 2005 at 179; emphasis added and citations omitted.) DMD treatments must be able to reach cardiac muscle as well as skeletal muscle, but cardiac muscle has proven resistant to AON uptake. (Exh. 2005 at 179.)

97. A review published in April 2014 states that "an improved understanding of the *in vivo* barriers to oligo delivery" is needed before large scale clinical successes can be obtained. (Exh. 2022 at 7.)

98. AONs with different chemical backbones have very different issues in terms of drug delivery. PS AONs are highly negatively charged and thus hydrophilic, yet must cross hydrophobic lipid bilayers to enter cells. (Exh. 2022 at 4.) For many years, researchers explored the use of carriers such as cationic lipids or other types of charge-neutralizing cationic polymers to facilitate cellular entry. While many of these compounds demonstrate efficacy *in vitro*, their *in vivo* utility is hampered by low efficacy, cost, and toxicity. (Exh. 2024 at 238 (quoted above); Exh. 2022 at 4.)

99. Another challenge with PS AON drug delivery results from their "stickiness," in that they bind many proteins tightly. These unintended interactions can significantly reduce the amount of AON reaching the nuclei of target tissues. (Exh. 2022 at 5.)

100. While theoretically one could compensate for inefficient delivery by increasing the dose administered, human clinical trials have highlighted several toxicities attributable to the chemical structure of AONs, including AONs with PS backbones. (Exh. 2027 at 73.) These include thrombocytopenia and hyperglycemia, activation of the complement and coagulation cascades, hypotension, and hepatocellular degradation. (Exh. 2027 at 74 and 78.) Thus, for

example, Trecovirsen, a PS AON intended to treat HIV, was unsuccessful in clinical trials because of dose limiting toxicities. (Exh. 2027 at 76.)

101. PNAs, another type of commonly used AONs, also suffer from poor cellular uptake. Except for the liver and kidneys, PNAs have relatively low uptake in normal tissue. While studies have attempted to elevate cellular uptake by conjugating PNAs to cell-penetrating positively charged peptides, uptake was only greater in cells overexpressing that particular mRNA. (Exh. 2029 at 186.)

3. Lack of animal models

102. Animal models in general are not useful for AON exon skipping validation because AONs are sequence specific. (Exh. 2015 at 10.)

103. This lack of reliable animal models has hindered development of exon skipping therapies for DMD. According to one 2011 paper, "[t]he lack of reliable systems for screening [AON] targeting many human dystrophin exons, especially the lack of animal models for establishing systemic efficacy poses a challenge for [AON] drug development." (Exh. 2015 at 2.)

104. The *mdx* mouse is one model used to evaluate therapies for DMD. These mice contain a nonsense mutation in exon 23 of the mouse dystrophin mRNA that causes premature termination of translation. (Exh. 2023 at 42.) However, because the mouse and human dystrophin genes have different nucleobase sequences, *mdx* mice cannot be used to test the efficacy of specific AON sequences against *human* dystrophin.

105. In order to target the human sequence directly, transgenic mice were developed carrying the full-size human *DMD* gene (hDMD). (Exh. 2024 at 233.) This is also a deficient model, however, because the mice do not have a dystrophic phenotype. (Exh. 2030 at 5906.) Researchers attempted to overcome this by crossbreeding this transgenic mouse with the *mdx*

mouse (hDMD/*mdx*), but expression of human dystrophin compensates for the deficiency in mouse dystrophin. (Exh. 2030 at 5906.) Thus, this mouse is also phenotypically normal. (Exh. 2015 at 10.) Because these mice do not display a dystrophic phenotype, one cannot assess drug delivery because delivery to healthy tissue differs from delivery to dystrophic tissue. As stated in one recent paper, "[t]his has prevented the animal model from being effective for testing AOs ..." (Exh. 2015 at 2.)

106. Even beyond the delivery issues, the *mdx* mouse and hDMD mouse are limited because exon skipping is assessed in a background where the spliceosome and other key participants in the splicing process are all encoded by mouse genes rather than human genes.

107. There are numerous parameters to optimize to obtain therapeutic exon skipping in humans. These include the choice of delivery compound (efficient delivery versus toxicity); oligochemistry (interaction with delivery compounds, affinity for target RNA sequence, intracellular stability, and degree of toxicity or immunogenicity); and administration method (intramuscular versus systemic). (Exh. 2024 at 238.)

108. Unfortunately, the cell culture and animal studies available to date are a poor proxy for human clinical trials. As stated in one 2010 publication, "predicting the amount of skipping needed *in vitro* for an AO to be therapeutic in a patient is impossible; the efficiency of exon skipping is likely to differ from patient to patient and mutation to mutation, and the levels of dystrophin protein restoration will depend on the quality of the muscle itself when a clinical treatment is started." (Exh. 2031 at 8.)

I. Human Clinical Trials to Date

109. Two companies, Sarepta Therapeutics Inc. (formerly AVI BioPharma Inc.) and Prosensa Holding N.V., are developing AONs to treat DMD for patients amenable to skipping exon 51 and exon 53. Clinical development of AONs is most advanced in the exon 51 patient

population. Sarepta's exon 51 skipping AON clinical candidate is eteplirsen (codename: AVI-4658). Prosensa's exon 51 skipping AON clinical candidate is drisapersen (codenames: PRO051; GSK2402968; GSK 968).

110. Sarepta's candidate, eteplirsen, is an exon 51-skipping morpholino AON having the following nucleobase sequence: CTCCAACATCAAGGAAGATGGCATTTCTAG that targets the pre-mRNA of exon 51 of the dystrophin gene. (Exh. 2032; Exh. 2033 at 3.) Results from an early single-blind, placebo-controlled clinical trial (registered as NCT00159250 at ClinicalTrials.gov) of eteplirsen were reported in 2009. (Exh. 2083.) Sarepta announced on August 15, 2011, the initiation of dosing of eteplirsen in a clinical efficacy study in the United States (ClinicalTrials.gov Identifier: NCT01396239, "the 201 Study"). (Exh. 2082.) The 201 Study was a double-blinded, placebo controlled Phase IIb study that enrolled 12 boys. Four boys were dosed eteplirsen at 30 mg/kg/week, four other boys were dosed eteplirsen at 50 mg/kg/week and the remaining four boys were dosed placebo. The primary biochemical endpoint to demonstrate efficacy in the 201 Study was percent dystrophin positive fibers. The secondary clinical endpoint to demonstrate efficacy in the 201 Study was the six-minute walk test ("6MWT"). A muscle biopsy was performed prior to dosing to determine the amount of dystrophin positive fibers at baseline. After 12 weeks of dosing the four boys in the 50 mg/kg/week group and two boys in the placebo group underwent a muscle biopsy to determine the amount of dystrophin positive fibers at this time. The boys in the 30 mg/kg/week group and two boys in the placebo group underwent a muscle biopsy after 24 weeks of dosing to determine the amount of dystrophin positive fibers at this time.

111. The 201 Study transitioned into a second human clinical trial in the United States that was registered on February 23, 2012 (ClinicalTrials.gov Identifier: NCT01540409, "the 202

Study"). The 202 Study, which is ongoing to date, is an open-label, long term safety and efficacy study. The primary endpoints to demonstrate efficacy in the 202 Study are the 6MWT and percent dystrophin positive fibers. Pulmonary function tests for maximum inspiratory pressure ("MIP") and maximum expiratory pressure ("MEP") are exploratory endpoints in the 202 Study. The same 12 boys who were in the 201 Study were enrolled in the 202 Study. The four boys who were dosed with placebo in the Study 201 Study were dosed with eteplirsen upon commencement of the 202 Study (*i.e.*, after 24 weeks after initial enrollment in the 201 Study). All 12 boys enrolled in the 202 Study underwent a muscle biopsy 48 weeks after initial enrollment in the 201 Study to determine the amount of dystrophin positive fibers at this time.

112. Based on the biopsies taken at Week 24 of the 201 Study, eteplirsen when dosed at 30 mg/kg/week produced a statistically significant increase in novel dystrophin-positive fibers (increase of 23% relative to baseline) whereas no such dystrophin increases were detected in the placebo dosed patients ($p \leq 0.002$). Even more significant increases in dystrophin were observed at Week 48 (52% and 43% in the 30 and 50 mg/kg/week cohorts, respectively). (Exh. 2058 at 640; Figure 2.) These data are evidence of eteplirsen meeting its clinical endpoint for dystrophin production. (Exh. 2058 at 639.)

113. Boys in the 201 Study and the 202 Study who were ambulant (*i.e.*, able to walk without assistance) underwent a 6MWT at three to six months regular intervals, including, but not limited to Week 48 and Week 144, the most recent week to date for which data has been reported. Two boys who were originally in the placebo control cohort in the 201 Study became non-ambulant (i.e., not able to walk without assistance) before Week 24 and remained so beyond Week 24 into the 202 Study. The remaining 10 ambulant boys who are able to perform the 6MWT represent the so-called modified Intent-To-Treat ("mITT") patient group and were

evaluated by the 6MWT at pre-determined intervals. At Week 48, the mITT patient group experienced a statistically significant 67.3 meter benefit compared to placebo/treatment delayed patients ($p \leq 0.001$). Through Week 48, eteplirsen was well tolerated with no treatment-related adverse events. (Exh. 2058 at 643; Figure 6; Exh. 2032; Exh. 2034.) Based on these data at Week 48, it was suggested that eteplirsen is safe and effective for the treatment of DMD in the exon 51 patient population. (Exh. 2058 at 644.) At Week 144, analysis of mean change from baseline distance walked in meters on the 6MWT for the mITT patient group demonstrated a significant difference in the adjusted mean change from baseline to Week 36 through Week 144 for the comparison of eteplirsen vs. placebo to eteplirsen. The adjusted mean change from baseline (375.6 meters) to Week 144 was −32.2 meters for the eteplirsen group; the change from baseline (394.5 meters) to Week 144 was −107.4 meters for the placebo to eteplirsen group. This translates into a statistically significant, clinically meaningful treatment benefit of 75.1 meters ($p \leq 0.004$) for the eteplirsen group over the placebo to eteplirsen group at Week 144. (Exh. 2059 at slide 9.) This most recent data available from the extension phase of the 202 Study reported at Week 144 reflects over two years of eteplirsen treatment for all boys in the 202 Study and almost three years of eteplirsen treatment for the boys who did not receive placebo in the 201 Study.

114. The 202 Study has also demonstrated to date that the boys dosed with eteplirsen on average have stable pulmonary function, based on MIP and MEP data obtained at Week 144 of the 202 Study. At Week 144, the MIP increased 14.7% relative to mean baseline value, and the MEP increased 12.8% relative to mean baseline value. Notably, these pulmonary measures were stable over 144 weeks in the two patients who experienced rapid decline in ambulation and were unable to complete the 6MWT. (Exh. 2059 at slide 14.)

115. Prosensa's drug candidate, drisapersen, is an exon 51 skipping 2'-Me-PS AON having the following nucleobase sequence: UCAAGGAAGAUGGCAUUUCU that targets the pre-mRNA of exon 51 of the dystrophin gene. (Exh. 2036 at 1515; Exh. 2037 at 987.) Drisapersen thus is structurally distinct from eteplirsen at least because: (i) drisapersen is 10 nucleobases shorter (20 versus 30); (ii) the drisapersen nucleobase sequence contains uracil bases (RNA-based) rather than thymine bases (DNA-based); and (iii) drisapersen has a different chemical backbone and internucleotide linkages given it is a 2'-Me-PS AON rather than a morpholino. Drisapersen is administered subcutaneously at 6 mg/kg, its maximum tolerated dose. (Exh. 2037 at 988; Exh. 2038 at 16.)

116. Prosensa entered into a strategic alliance in 2009 with GlaxoSmithKline ("GSK"), a significant global pharmaceutical company, to develop drisapersen (GSK '968) for an undisclosed sum. (Exh. 2060.) In the context of announcing the initiation of a Phase III study of drisapersen, GSK's Head of Development and Chief Medical Officer stated it "is an important milestone." At the same time, Prosensa's Chief Medical Officer stated, "[i]f the results of this study are positive, we hope it will lead to an approved treatment option for thousands of young people worldwide living with this devastating disease." (Exh. 2060.)

117. After investing more than two and a half years effort and expenses, GSK and Prosensa announced that the primary endpoint in its Phase III double-blinded, placebo controlled trial was not met. Specifically, patients dosed with drisapersen did not demonstrate a statistically significant improvement in the 6MWT compared to placebo. (Exh. 2039.) In the Prosensa Phase III study, 186 boys were randomized to either a first cohort of 125 patients that were administered drisapersen at a dose of 6 mg/kg/week for 48 weeks or a second cohort of 61 patients. In addition to not demonstrating a statistically significant effect in the 6MWT

compared to placebo, there were also no treatment differences in key secondary assessments of motor function. Also, a significant proportion of adverse events were also reported: injection site reactions (78% for drisapersen versus 16% for placebo) and renal toxicity including subclinical proteinuria (46% for drisapersen versus 25% for placebo). At the time of reporting these data, GSK's Senior Vice President and Head of Rare Diseases Research & Development stated, "[w]e are committed to evaluating the outcome of this study in the context of the overall development programme with experts in the field, and we expect such evaluation to help inform our next steps for drisapersen." (Exh. 2039.) At the same time, it was announced that a "[f]ull evaluation of the benefit-to-risk profile of drisapersen across all studies is anticipated to be completed by year end [2013]. This many include analyses of pooled results from various drisapersen studies." (Exh. 2039.)

118. Almost four months after the prior announcement, GSK's Senior Vice President and Head of Rare Diseases Research & Development stated, "[w]e have completed our review…of the drisapersen data…." and announced that it was terminating the collaboration agreement between GSK and Prosensa. (Exh. 2040.)

119. Prosensa is continuing to investigate the possibility of some benefit for young, relatively healthy patients (≥5 years of age; time to rise from floor ≤7 s). (Exh. 2037 at 987.) In a report on a later phase II study, the authors suggest some possible improvement at week 25. (Exh. 2037 at 987.) Although the investigators detected some increase in mean dystrophin concentration in patients treated with drisapersen, "the differences were small and there was no linear correlation with clinical outcome data." (Exh. 2037 at 993.) Moreover, "[p]atients given drisapersen reported more adverse events related to injection-site reactions and renal events

(subclinical proteinuria) than did those given placebo. Injection-site reactions were reported despite injection site rotation throughout the study." (Exh. 2037 at 993-94.)

V. AZL U.S. APPLICATION NOS. 11/233,490, 13/550,210, 14/198,992 and 14/248,279

120. I understand that an interference (Patent Interference No. 106,007) has been declared between UWA's U.S. Patent No. 8,455,636 and AZL's U.S. Application No. 11/233,495, which published as U.S. Patent Application Publication US 2006/0147952. (Exh. 2041, cover page.) In my declaration, I will refer to this AZL application as the '495 application, and when citing to the '495 application I will cite to Exh. 2041.

121. The '495 application was filed on September 21, 2005. *Id.*, cover page. It states in the '495 application that "This application is a continuation of PCT International Patent Application No. PCT/NL2003/000214, filed on Mar. 21, 2003...." (Exh. 2041 at [0001].) I have been told that a "continuation application" is a later-filed application that has the same disclosure as an earlier-filed application. Thus, I understand that the disclosure in the '495 application is essentially the same as the disclosure in PCT/NL2003/000214. (Exh. 2042.) My review of the '495 application and PCT/NL2003/000214 confirms my understanding that their disclosures are essentially the same.

122. I understand that a second interference (Patent Interference No. 106,008) has been declared between UWA's U.S. Patent Nos. 7,807,816 and 7,960,541 and AZL's U.S. Application No. 13/550,210, which published as U.S. Patent Application Publication US 2013/0072671. (Exh. 2043, cover page.) In my declaration, I will refer to this AZL application as the '210 application, and when citing to the '210 application I will cite to Exh. 2043.

123. The '210 application was filed on July 16, 2012. (Exh. 2043, cover page.) It states in the '210 application that "This application is a continuation of patent application Ser.

No. 11/233,495, filed Sep. 21, 2005, pending, which is a continuation of PCT International Patent Application No.PCT/NL2003/000214, filed on Mar. 21, 2003...." (Exh. 2043 at [0001].)

124. However, an updated filing receipt mailed December 11, 2012, indicates that the '210 "application is a CON [I understand this means "continuation"] of 12/976,381 12/22/10 which is a CON of 12/198,007 08/25/2008 PAT 7534879 which is a CON of 11/233,495 09/21/2005[.]" (Exh. 2044.) Because the '210 application is a "continuation" of continuations relating to the '495 application my understanding is that the disclosure in the '210 application is essentially the same as the disclosure in the '495 application. My review of the '210 application confirms this.

125. I understand that a third interference (Patent Interference No. 106,013) has been declared between UWA's U.S. Patent No. 8,486,907 and AZL's U.S. Application No. 14/198,992, which published as U.S. Patent Application Publication US 2014/0275212. (Exh. 2052, cover page.) In my declaration, I will refer to this AZL application as the '992 application, and when citing to the '992 application I will cite to Exh. 2052.

126. The '992 application was filed on March 6, 2014. (Exh. 2052, cover page.) It states in the '992 application that "[t]his application is a continuation of patent application Ser. No. 13/550,210, filed Jul. 16, 2012, which is a continuation of patent application Ser. No. 12/976,381, filed Dec. 22, 2010, which is a continuation of U.S. patent application Ser. No. 12/198,007, filed Aug. 25,2008, now U.S. Pat. No. 7,534,879, which is a continuation of patent application Ser. No. 11/233,495, filed on Sep. 21, 2005, which claims the benefit of International Patent Application No. PCT/NL2003/000214, filed Mar. 21, 2003." (Exh. 2044 at [0001].) Because the '992 application is a "continuation" of the '210 application my understanding is that the disclosure in the '992 application is essentially the same as the disclosure in the '210

application, and therefore also essentially the same as the disclosure in the ’495 application. My review of the ’992 application confirms this.

127. I have also been asked to consider the claims in AZL’s U.S. Patent Application No. 14/248,279, which published as U.S. Patent Application Publication US 2014/0213635. (Exh. 2035, cover page.) In my declaration, I will refer to this AZL application as the ’279 application and when citing to the ’279 application I will cite to Exh. 2035.

128. The ’279 application was filed on April 8, 2014. (Exh. 2035, cover page.) It states in the ’279 application that it is a continuation of the ’495 application. (Exh. 2035 at [0001].) Because the ’279 application is a “continuation” of the ’495 application my understanding is that the disclosure in the ’279 application is essentially the same as the disclosure in the ’495 application. My review of the ’279 application confirms this.

129. Thus, the disclosures of the ’495, ’210, ’992, and ’279 applications are essentially the same. I will refer to these four applications collectively as the AZL applications. For the sake of simplicity, in this declaration, when I cite to the disclosure in the AZL applications I will cite only to U.S. Patent Application Publication US 2006/0147952 (Exh. 2041) with the understanding that the same disclosure is also contained in the ’210, ’922, and ’279 applications.

A. The Disclosure of the AZL Applications

130. The AZL applications are directed to AONs and methods of using them for human clinical indications. For example, the following description of the “TECHNICAL FIELD” is provided: “[t]he invention relates to the fields of molecular biology and medicine. More in particular, the invention relates to the restructuring of mRNA produced from pre-mRNA, and therapeutic uses thereof.” (Exh. 2041 at [0002].)

131. Consistent with this, the invention is disclosed as relating to the ability to influence the processing of pre-mRNA:

> Although much is known about the actual processes involved in the generation of an mRNA from a pre-mRNA, much also remains hidden. In the present invention it has been shown possible to influence the splicing process such that a different mRNA is produced. The process allows for the predictable and reproducible restructuring of mRNA produced by a splicing machinery. An oligonucleotide capable of hybridizing to pre-mRNA at a location of an exon that is normally included in the mature mRNA can direct the exclusion of the thus targeted exon or a part thereof.

(Exh. 2041 at [0005].)

132. The AZL applications provide a definition for the term "exon":

> An exon according to the invention is a sequence present in both the pre-mRNA and mRNA produced thereof, wherein the sequence included in the mRNA is, in the pre-mRNA, flanked on one side (first and last exon) or both sides (any other exon then the first and the last exon) by sequences not present in the mRNA.

(Exh. 2041 at [0010].)

133. Paragraphs [0006]-[0009] of the AZL applications purport to provide guidance on how to design AONs that are intended to induce exon skipping. Paragraph [0006] begins:

> In the present invention, means and methods are provided for the design of appropriate complementary oligonucleotides. To this end, the invention provides a method for generating an oligonucleotide comprising determining, from a (predicted) secondary structure of RNA from an exon, a region that assumes a structure that is hybridised to another part of said RNA (closed structure) and a region that is not hybridised in said structure (open structure), and subsequently generating an oligonucleotide, which at least in part is complementary to said closed structure and which at least in part is complementary to said open structure. RNA molecules exhibit strong secondary structures, mostly due to base pairing of complementary or partly complementary stretches within the same RNA.

(Exh. 2041 at [0006].)

134. The paragraph goes on to refer to an "exon inclusion signal":

> Without being bound by theory, it is believed that the secondary structure of the RNA of an exon plays a role in structuring the splicing process. Through its structure, an exon is recognized as a part that needs to be included in the pre-mRNA. Herein this signalling function is referred to as an **exon inclusion signal**. A complementary oligonucleotide of the invention is capable of interfering with the structure of the exon and thereby capable of interfering with the exon inclusion signal of the exon. It has been found that many complementary

> oligonucleotides indeed comprise this capacity, some more efficient than others. **Oligonucleotides of the invention, i.e. those with the said overlap directed toward open and closed structures in the native exon RNA, are a selection from all possible oligonucleotides….** Without being bound by theory it is thought that the overlap with an open structure improves the invasion efficiency of the oligonucleotide (i.e. increases the efficiency with which the oligonucleotide can enter the structure), whereas the overlap with the closed structure subsequently increases the efficiency of interfering with the secondary structure of the RNA of the exon, and thereby interfere with the exon inclusion signal. It is found that the length of the partial complementarity to both the closed and the open structure is not extremely restricted.

(Exh. 2041 at [0006]; emphasis added.)

135. The focus on the "open" and "closed" secondary structure of the RNA is also evident from the claims in the '495 application as published. For example, claim 1 is for a method of generating an oligonucleotide:

> 1. A method for generating an oligonucleotide or an equivalent thereof comprising:
>
> determining from a secondary structure of RNA from an exon, a region that assumes a structure that is hybridized to another part of said RNA (closed structure) and a region that is not hybridized in said structure (open structure); and
>
> generating said oligonucleotide or said equivalent thereof, of which at least part of said oligonucleotide or said equivalent thereof is complementary to said closed
>
> structure and of which at least another part of said oligonucleotide or said equivalent thereof is complementary to said open structure.

(Exh. 2041 at 22.)

136. Claim 15 of the published '495 application is for "[a]n oligonucleotide or an equivalent thereof obtainable by a method according to claim 1." (Exh. 2041 at page 22.)

137. "Complementarity" is given a specific meaning in the AZL applications: "[t]he term complementarity is used herein to refer to a stretch of nucleic acids that can hybridise to another stretch of nucleic acids under physiological conditions. It is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the

opposing strand." (Exh. 2041 at [0006].) In other words, the AZL applications disclose that a "complementary" AON may contain nucleobases that are mismatches that do not Watson-Crick base pair with the target stretch of nucleic acids. However, no example of an AON (not even a 2'-O-Me-PS) containing a "mismatch" versus its target sequence is disclosed in the AZL application.

138. In the context of mismatches and complementarity, the AZL applications state that "[i]t is thought that higher hybridisation strengths, (i.e. increasing number of interactions with the opposing strand) are favourable in increasing the efficiency of the process of interfering with the splicing machinery of the system." (Exh. 2041 at [0006].)

139. To identify "open" and "closed" secondary structure in pre-mRNA, the AZL applications point to known structure modeling programs:

> The secondary structure is best analysed in the context of the pre-mRNA wherein the exon resides. Such structure may be analysed in the actual RNA.
>
> However, it is currently possible to predict the secondary structure of an RNA molecule (at lowest energy costs) quite well using structure-modelling programs. A non-limiting example of a suitable program is RNA mfold version 3.1 server (Mathews et al 1999, J. Mol. Biol. 288: 911-940). A person skilled in the art will be able to predict, with suitable reproducibility, a likely structure of the exon, given the nucleotide sequence. Best predictions are obtained when providing such modelling programs with both the exon and flanking intron sequences. It is typically not necessary to model the structure of the entire pre-mRNA.

(Exh. 2041 at [0007] and [0008].)

140. The AZL applications provide some additional guidance in AON design for exon skipping based on the predicted secondary structure of the pre-mRNA:

> The open and closed structure to which the oligonucleotide is directed, are preferably adjacent to one another. It is thought that in this way the annealing of the oligonucleotide to the open structure induces opening of the closed structure, annealing progresses into this closed structure. Through this action the previously closed structure assumes a different conformation. The different conformation may result in the disruption of the exon inclusion signal.

(Exh. 2041 at [0009].)

141. In terms of targeting the AON in the pre-mRNA, the AZL applications also inform the reader that "An oligonucleotide of the invention typically does not have to overlap with a splice donor or splice acceptor of the exon." (Exh. 2041 at [0020].) In other words, AONs disclosed in the AZL applications do not cross a splice junction.

142. The AZL applications then relate the concept of AON-induced exon skipping to specific indications, one of which is restructuring dystrophin mRNA in DMD patients. (Exh. 2041 at [0012]-[0015].)

143. The AZL applications explain that:

> By the targeted skipping of a specific exon, a DMD phenotype can be converted into a milder BMD phenotype. The skipping of an exon can be induced by the binding of antisense oligoribonucleotides (AONs) targeting either one or both of the splice sites, or exon-internal sequences. Since an exon will only be included in the mRNA when both the splice sites are recognised by the spliceosome complex, splice sites are obvious targets for AONs. This was shown to be successful, albeit with variable efficacy and efficiency (17, 18, 20, 21).

(Exh. 2041 at [0015].)

144. In the context of DMD, the AZL applications go on to state:

> We hypothesised that targeting exon-internal sequences might increase specificity and reduce interference with the splicing machinery itself. Some exons have weak splice sites and appear to require binding of a SR protein to an exon recognition sequence (ERS) or an exonic splicing enhancer (ESE) to be properly recognised by the splicing machinery (24)…. In contrast to the previous opinion that skipping can only be achieved with weak splice sites or exons containing ERS-like sequences, we have seen that of the exons that were skipped in the present invention most do not have weak splice sites nor do they contain ERS-like sequences. Thus binding of the AONs to the targeted exon per se is sufficient to cause exon skipping, either by interfering with one or more components of the splicing machinery or by altering the secondary structure of the RNA in such a manner that the splicing machinery no longer recognizes the exon.

(Exh. 2041 at [0015].)

145. AONs "fulfilling the requirements of the invention" are described:

> Any oligonucleotide fulfilling the requirements of the invention may be used to induce exon skipping in the DMD gene. In a preferred embodiment an oligonucleotide comprises a sequence as depicted as active in exon-skipping in table 2, or a functional equivalent thereof comprising a similar, preferably the same hybridisation capacity in kind, not necessarily in amount. Preferably an oligonucleotide comprising a sequence as depicted in table 2, derived from the exons 2, 40, 41, 42, 43, 44, 45, 49, 50, 51 or 53, demonstratably active in exon skipping.

(Exh. 2041 at [0016].)

146. Further information about the AONs is provided in paragraph [0018]:

> The complementary oligonucleotide generated through a method of the invention is preferably complementary to a consecutive part of between 16 and 50 nucleotides of said exon RNA. Different types of nucleic acid may be used to generate the oligonucleotide. Preferably, the oligonucleotide comprises RNA, as RNA/RNA hybrids are very stable. Since one of the aims of the exon skipping technique is to direct splicing in subjects it is preferred that the oligonucleotide RNA comprises a modification providing the RNA with an additional property, for instance resistance to endonucleases and RNaseH, additional hybridisation strength, increased stability (for instance in a bodily fluid), increased or decreased flexibility, reduced toxicity, increased intracellular transport, tissue-specificity, etc. Preferably said modification comprises a 2'-O-methyl-phosphorothioate oligoribonucleotide modification.

(Exh. 2041 at [0018].)

147. Other chemical backbones are mentioned:

> With the advent of nucleic acid mimicking technology it has become possible to generate molecules that have a similar, preferably the same hybridisation characteristics in kind not necessarily in amount as nucleic acid itself. Such equivalents are of course also part of the invention. Examples of such mimics equivalents are peptide nucleic acid, locked nucleic acid and/or a morpholino phosphorodiamidate…. Hybrids between one or more of the equivalents among each other and/or together with nucleic acid are of course also part of the invention.

(Exh. 2041 at [0019].)

148. The AZL applications disclose the context in which the exon-skipping AONs are applied:

> Any cell may be used, however, as mentioned, a preferred cell is a cell derived from a DMD patient. Cells can be manipulated in vitro, i.e. outside the subject's

> body. However, ideally the cells are provided with a restructuring capacity in vivo. Suitable means for providing cells with an oligonucleotide, equivalent or compound of the invention are present in the art. Improvements in these techniques are anticipated considering the progress that has already thus far been achieved. Such future improvements may of course be incorporated to achieve the mentioned effect on restructuring of mRNA using a method of the invention.

(Exh. 2041 at [0026].)

149. The AZL applications goes on to state:

> At present suitable means for delivering an oligonucleotide, equivalent or compound of the invention to a cell in vivo comprise, polyethylenimine (PEI) or synthetic amphiphils (SAINT-18) suitable for nucleic acid transfections. The amphiphils show increased delivery and reduced toxicity, also when used for in vivo delivery.

(Exh. 2041 at [0026].)

150. There are four examples in the AZL applications. In Example 1, a limited number of AONs were tested by RT-PCR in cells derived from six DMD patients with different mutations to determine if the AONs would induce exon skipping. The mutations, targeted exons, and AONs, are set forth in Table 1. (Exh. 2041 at 14.) A single AON was tested for each of exon 51 and exon 53.

151. Exon skipping was assessed *in vitro* using myotube cultures. (Exh. 2041 at [0041].) In this model, primary human myoblasts obtained from DMD patients having known mutations in their DMD gene are cultured to confluency, and then myotube formation is induced by additional culturing under a condition of serum deprivation. (Exh. 2041 at [0041].) The myotubes were then transfected with AONs using polyethylimine ("PEI"), which as explained above is a cationic polymer that facilitates transfection. (Exh. 2041 at [0041].)

152. To determine if the AONs achieved exon skipping in the transfected myotubes, the investigators performed an RT-PCR analysis on mRNA obtained from myotubes at 24 hours post-transfection. (Exh. 2041 at [0031], [0042], and Fig. 1.) According to the investigators, "In

all patients, the targeted exons were skipped at high efficiencies, and precisely at the exon boundaries, as confirmed by sequence analysis of the novel shorter transcripts (FIG. 1)." (Exh. 2041 at [0031].)

153. The investigators also analyzed dystrophin production in the transfected myotubes, reporting that "immunohistochemical analysis of transfected myotube cultures detected dystrophin in the majority of myotubes for each patient (FIG. 2)." (Exh. 2041 at [0032].) From the experiments performed in Example 1, the investigators conclude that "[f]ollowing AON treatment, we show for each patient the precise skipping of the targeted exon on RNA level, and a dystrophin protein in 75% to 80% of the treated myotubes." (Exh. 2041 at [0034].)

154. Only *in vitro* experiments are disclosed in Example 1.

155. Example 2 discloses experiments relating to " [a] series of AONs (two per exon, see Table 2) … designed to bind to exon-internal target sequences showing a relatively high purine-content and, preferably, an open secondary pre-mRNA structure (at 37^{o} C.), as predicted by the RNA mfold version 3.1…." (Exh. 2041 at [0047].) All of the AONs used in Example 2 were synthesized with "a full-length phosphorothioate backbone and 2'-O-methyl modified ribose molecules…." (Exh. 2041 at [0047].)

156. Table 2 provides the nucleotide sequences of the AONs:

TABLE 2

Characteristics of the AONs used to study the targeted skipping of 15 different DMD exons[a]

SEQ ID NO:	Name	Antisense sequence (5'-3')	Length (bp)	G/C %	U/C %	Exon skip	Transcript
1	h2AON 1	cccauuuugugaauguuuucuuuu	24	29	75	+	OF
2	h2AON 2	uugugcauuuacccauuuugug	22	36	68	-	OF
3	h29AON 1	uauccucugaaugucgcauc	20	45	65	+	IF
4	h29AON 2	gguuauccucugaaugucgc	20	50	60	+	IF
5	h40AON 1	gagccuuuuuucuucuuug	19	37	79	+	IF
6	h40AON 2	uccuuucgucucugggcuc	19	58	79	+	IF
7	h41AON 1	cuccucuuucuucuucugc	19	47	95	+	IF
8	h41AON 2	cuucgaaacugagcaaauuu	20	35	50	+	IF
9	h42AON 1	cuugugagacaugagug	17	47	41	+	IF
10	h42AON 2	cagagacuccucuugcuu	18	50	67	+	IF
11	h43AON 1	ugcugcugucuucuugcu	18	50	78	-	OF
12	h43AON 2	uuguuaacuuuuucccauu	19	26	79	+	OF
13	h44AON 1	cgccgccauuucucaacag	19	58	63	+	OF
14	h44AON 2	uuuguauuuagcauguuccc	20	35	70	+	OF
15	h45AON 1	gcugaauuauuucuucccc	19	42	74	-	OF
16	h45AON 5	gcccaaugccauccugg	17	65	58	+	OF
17	h46AON 4b	cugcuuccuccaacc	15	60	80	+	OF
18	h46AON 8b	gcuuuucuuuuaguugcugc	20	40	75	+	OF
19	h47AON 1	ucuugcucuucugggcuu	18	50	78	-	IF
20	h47AON 2	cuugagcuuauuuucaaguuu	21	29	67	-	IF
21	h48AON 1	uuucuccuuguuucuc	16	38	94	-	IF
22	h48AON 2	ccauaaauuuccaacugauuc	21	33	62	-	IF
23	h49AON 1	cuuccacauccgguuguuu	19	47	74	+	IF
24	h49AON 2	guggcugguuuuuccuugu	19	47	68	+	IF
25	h50AON 1	cucagagcucagaucuu	17	47	59	+	OF
26	h50AON 2	ggcugcuuugcccuc	15	67	73	-	OF
27	h51AON 1	ucaaggaagauggcauuucu	20	40	45	+	OF
28	h51AON 2	ccucugugauuuuauaacuugau	23	30	65	+	OF
29	h53AON 1	cuguugccuccgguucug	18	61	72	+	OF
30	h53AON 2	uuggcucuggccuguccu	18	61	72	-	OF

[a]Two AONs were tested per exon. Their different lengths and G/C contents (%) did not correlated to their effectivity in exon skipping (1, induced skipping, 2, no skipping). The AONs were directed to purine (A/G) -rich sequences as indicated by their (antisense) U/C content (%). Skipping of the target exons resulted in either an in-frame (IF) or an out-of-frame (OF) transcript.
b van Deutekom et al., 2001 [21].

(Exh. 2041 at [0153].)

157. Although there are 30 AONs disclosed in Table 2, only two AONs are designed to induce skipping of exon 51. AON "h51AON1," which is identified in Table 2 as SEQ ID NO: 27, and was also used in Example 1, is 20 nucleotides in length and is indicated as being positive for exon skipping. AON "h51AON2," which is also identified as SEQ ID NO: 28, is 23 nucleotides in length. It also is indicated as being positive for skipping of exon 51.

158. Table 2 only discloses two AONs designed to induce skipping of exon 53. The AON designated "h53AON1," which is identified as SEQ ID NO: 29, and was also used in Example 1, is 18 nucleotides in length. According to Table 2, this AON does induce skipping of exon 53. On the other hand, "h53AON2," which is also identified as SEQ ID NO: 30, is also 18 nucleotides long, but it did not induce skipping of exon 53.

159. Exon skipping was assessed in Example 2 by using *in vitro* experiments. No *in vivo* studies were reported in Example 2. Myotubes were obtained from myoblast cultures of human primary myoblasts isolated from a normal individual, that is, an individual not diagnosed with DMD. (Exh. 2041 at [0048].) The AONs disclosed in Table 2 were transfected into myotube cultures using PEI. (Exh. 2041 at [0051].) At a point 24 hours post-transfection, "transcripts were analysed by RT-PCR using different primer combinations encompassing the targeted exons (Table 3)." (Exh. 2041 at [0051].) Fig. 5 shows the results of the RT-PCR analysis. (Exh. 2041 at [0051] and [0095].)

160. According to the investigators, "[o]f the 30 AONs tested, a total of 21 (70%) reproducibly generated shorter transcript fragments with sizes corresponding to the specific skipping of the targeted exons (FIG. 5 and Table 2)." (Exh. 2041 at [0051].) The AONs tested varied from 15 to 24 nucleotides in length, with G/C contents between 26 and 67%. (Exh. 2041

at [0047].) According to the applications, "[t]heir different lengths and G/C contents (%) did not correlate to their effectivity in exon skipping." (Exh. 2041 at Table 2.) Dystrophin protein production is not disclosed in Example 2.

161. Example 3 discloses *in vitro* experiments designed to demonstrate to double exon skipping, that is, skipping of two exons to restore the reading frame of the dystrophin mRNA in cells obtained from two DMD patients. (Exh. 2041 at [0082].) The mutations, skipped exons, and AONs used in this experiment are identified in Table 5. (Exh. 2041 at [0156].) Four of the AONs used in this series of experiments were also described in Table 2, which I have addressed previously.

162. There is no information in Example 3 that provides guidance on designing AONs capable of inducing exon skipping.

163. Using myotube cultures of cells derived from the two DMD patients, the investigators report that their data "demonstrated the feasibility of specific double-exon skipping in both samples…." (Exh. 2041 at [0082].) Detection of exon skipping was measured using RT-PCR. (Exh. 2041 at [0082] and [0086].) Dystrophin protein production is not reported for this Example.

164. Example 4 discloses experiments designed to test the capability to induce exon skipping by transfecting a vector system into target cells. (Exh. 2041 at [0088].) The vector, which is a recombinant adeno-associated viral (rAAV) vector (Exh. 2041 at [0090]), includes sequences that permit expression of antisense sequences that had been shown to induce skipping of mouse exon 46. (Exh. 2041 at [0089].) Although no data are shown, the investigators report that "[h]igh titre virus productions were effective in inducing exon skipping." (Exh. 2041 at [0090].)

165. There is no information in Example 4 that provides guidance on designing AONs capable of inducing exon skipping.

166. The AZL applications do not disclose any clinical trial results, do not disclose any clinical study demonstrating the ability of the AONs directed to skipping of exons 51 or 53 (or for that matter, to any exon), and do not disclose restoration of dystrophin production in patients with DMD.

B. The Declarations of Interference

167. I have been informed that Patent Interference No. 106,007 has been declared between AZL's '495 application and UWA's U.S. Patent No. 8,455,636, which I will refer to as the '636 patent. I have also been informed that the count in this interference, which defines the subject matter at issue, is claim 15 of the '495 application or claim 1 of the '636 patent. Claim 15 of the '495 application reads:

> 15. An isolated antisense oligonucleotide of 15 to 80 nucleotides comprising at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1.)

168. Claim 1 of the '636 patent reads:

> 1. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length comprising at least 20 consecutive nucleotides of SEQ ID NO:193, wherein the oligonucleotide specifically hybridizes to an exon 53 target region of the human dystrophin gene inducing exon 53 skipping, and wherein the uracil bases are optionally thymine bases.

(Exh. 2046 at column 131, lines 49-54.)

169. I have been informed that Patent Interference No. 106,008 has been declared between AZL's '210 application and UWA's U.S. Patent Nos. 7,807,816 and 7,960,541, which I

will refer to as the '816 patent and the '541 patent, respectively. I have also been informed that the count in this interference is claims 11 or 19 of the '210 application, or claim 1 of the '816 patent, or claim 1 of the '541 patent. Claims 11 and 19 of the '210 application read:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a morpholine ring, wherein said oligonucleotide is capable of binding to an exon internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.
>
> 19. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a 2'-*O*-methyl ribose moiety, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) 1 (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

(Exh. 2047 at 1 and 2.)

170. Claim 1 of the '816 patent reads:

> 1. An isolated antisense oligonucleotide of 30 to 50 nucleotides in length comprising SEQ ID NO: 181, wherein the uracil bases are optionally thymine bases.

(Exh. 2048 at column 129, lines 2-4.)

171. SEQ ID NO: 181 is cuccaacaucaaggaagauggcauuucuag. (Exh. 2048 at column 117.)

172. Claim 1 of the '541 patent reads:

> 1. An isolated antisense oligonucleotide of 25 to 50 nucleotides in length comprising SEQ ID NO: 180, wherein the uracil bases are optionally thymine bases.

(Exh. 2049 at column 119, lines 11-13.)

173. SEQ ID NO: 180 is acaucaaggaagauggcauuucuag. (Exh. 2049 at column 107.)

174. I have been informed that Patent Interference No. 106,013 has been declared between AZL's '992 application and UWA's U.S. Patent No. 8,486,907, which I will refer to as

the ’907 patent. I have also been informed that the count in this interference is claim 1 of the ’992 application or claims 1, 19, 22, or 25 of the ’907 patent. Claim 1 of the ’991 application reads:

> 1. A method for inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 20 to 50 nucleotides in length to a cell, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1
>
> (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon internal sequence.

(Exh. 2050 at 1.)

> 175. Claims 1, 19, 22, and 25 of the ’907 patent read:
>
> 1. A method of inducing skipping of exon 51 in a dystrophin gene in a subject comprising administering a pharmaceutical composition comprising an antisense oligonucleotide of 30 to 50 nucleotides in length comprising SEQ ID NO: 181, wherein the uracil bases are optionally thymine bases, and a pharmaceutically acceptable carrier.
>
> 19. A method of correcting a defective gene for dystrophin in a subject comprising administering a pharmaceutical composition comprising an antisense oligonucleotide of 30 to 50 nucleotides in length comprising SEQ ID NO: 181, wherein the uracil bases are optionally thymine bases, and a pharmaceutically acceptable carrier.
>
> 22. A method of restoring or increasing functional dystrophin protein production in a subject comprising administering a pharmaceutical composition comprising an antisense oligonucleotide of 30 to 50 nucleotides in length comprising SEQ ID NO: 181, wherein the uracil bases are optionally thymine bases, and a pharmaceutically acceptable carrier.
>
> 25. A method of treating muscular dystrophy associated with a defective gene for dystrophin in a subject comprising administering a pharmaceutical composition comprising an antisense oligonucleotide of 30 to 50 nucleotides in length comprising SEQ ID NO: 181, wherein the uracil bases are optionally thymine bases, and a pharmaceutically acceptable carrier.

(Exh. 2051 at columns 137 and 138.)

176. SEQ ID NO: 181 is cuccaacaucaaggaagauggcauuucuag. (Exh. 2051 at column 125.)

177. I understand that AZL's '279 application has claims that are not currently involved in an interference, but which may become involved in one. I have been asked to consider these claims as part of the analyses provided in my declaration.

C. The Person of Ordinary Skill in the Art

178. I understand that many issues in U.S. patent law, including written description, enablement, and indefiniteness, are assessed from the perspective of the hypothetical person of ordinary skill in the art. I understand that many of the issues I have been asked to consider take into account the level of skill and knowledge possessed by a person of ordinary skill in the art at the time of the invention. I have been informed that the relevant time is March 21, 2003, which is the date that AZL filed its earliest patent application, although my opinions would not change if the date were the filing dates of any of the later-filed U.S. AZL applications at issue in the interferences. (Exh. 2042).

179. A person of ordinary skill in the art would have a Ph.D. degree in cell biology, genetics, molecular biology, or an equivalent, and several years of experience with AONs for inducing exon skipping, including familiarity with *in vitro* and *in vivo* methods for testing the safety and efficacy of such AONs. Further, a person of ordinary skill in this art would have at least some knowledge of, and experience with, chemical modifications that may be incorporated into AONs, such as modifications to the backbone and/or nucleobases of the AONs, and the impact of those modifications on the utility of the AONs. The person of ordinary skill in the art would also have at least some understanding of the use of AONs for inducing exon skipping in the context of medical conditions, such as DMD, that may be treated by administering such AONs.

180. For simplicity, I may refer to a person of ordinary skill in the art as a "skilled person."

VI. AZL'S CLAIMS INVOLVED IN THE INTERFERENCES

181. I have been informed that claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103 of the '495 application are involved in Interference No. 106,007. All of these claims are directed to AONs "capable of binding" to exon 53 of the human dystrophin pre-mRNA (claims 78-79, 84, 86, 88-90, 97-98, 101-103) and/or "comprising" certain sequences from exon 53 of the human dystrophin pre-mRNA (claims 15 and 76-77, 80, 82, 84, 86, 88-90, 98, 101 and 102) and inducing skipping of that exon.

182. Attached as Appendix B to my declaration is a copy of "ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES" (Exh. 2045) that I understand was submitted by AZL in the interference and lists all of AZL's involved claims.

183. I have been informed that claims 11, 12, 14, 15, 17-29 of the '210 application are involved in Interference No. 106,008. All of these claims are directed to AONs "capable of binding" to exon 51 of the human dystrophin pre-mRNA and inducing skipping of that exon.

184. Attached as Appendix C to my declaration is a copy of "ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES" (Exh. 2047) that I understand was submitted by AZL in the interference and lists all of AZL's involved claims.

185. I have been informed that claims 1-7 and 10-27 of the '992 application are involved in Interference No. 106,013. All of these claims are directed to methods of using AONs "capable of binding to exon 51" of the human dystrophin pre-mRNA and inducing skipping of that exon.

186. Attached as Appendix D to my declaration is a copy of "ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES" (Exh. 2050) that I understand was submitted by AZL in the interference that lists all of AZL's involved claims.

187. I have also been asked to review and offer my opinions on claims 1-16 and 20-26 in AZL's '279 application. Attached as Appendix E to my declaration is a copy of an "AMENDMENT UNDER 37 CFR §1.312- NOTICE OF ALLOWANCE MAILED" (Exh. 2053) that lists the claims in that application.

188. There are two general types of claims in the AZL applications: (1) the "comprising" claims, found only in the '495 application, which require a minimal nucleobase sequence, and (2) the "capable of binding claims," found in all four AZL applications, which do not. As discussed below, all of the claims encompass an enormous number of chemical compounds.

A. Interpretation of the Claims in the '495 Application

1. The "comprising" claims

189. Claims 15 reads as follows:

> 15. An isolated antisense oligonucleotide of 15 to 80 nucleotides comprising at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.[3]

(Exh. 2045 at 1.)

[3] I have been informed that the parties have recognized there is a typographical error in claim 15, specifically, 2'-*O*-methyl-, phosphorothioate should read 2'-*O*-methyl-phosphorothioate. The typographical error does not appear in claim 76.

190. I have been informed that in an interference the words in the patent claims are interpreted broadly and consistently with the typical meaning of the words as understood by a person of ordinary skill in the art, unless it is clear from reading the application that an atypical meaning is intended. I have applied this approach in addressing certain of the words in AZL's claims. I have not attempted to address every word appearing in AZL's claims because not all of the words are relevant to my opinions expressed in this declaration. Moreover, some of the claim terms have well understood meanings to a person of ordinary skill in the art, which are unlikely to be disputed by the parties. For example, I consider "antisense oligonucleotide" to have a well understood meaning. In the event that AZL or its expert(s) offer an interpretation for a claim term that I have not interpreted, I reserve the right to provide my views on the proper interpretation of such terms if I disagree with AZL's interpretation.

191. According to claim 15, the AON is "of 15 to 80 nucleotides" and comprises "at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29)." A person of ordinary skill in the art would understand this to mean that the overall length of the AON ranges from a minimum of 15 nucleotides up to a maximum of 80 nucleotides. Regardless of the overall length of the AON (within the 15-80 range), it must include at least 15 nucleobases of the 18 bases in the sequence "cuguugccuccgguucug." Because the 15 nucleobases need not be consecutive, there can be one or more "mismatches" between this portion of the AON and exon 53 of the dystrophin pre-mRNA. The nucleobase sequence of the remaining nucleotides is undefined.

192. There are a tremendous number of compounds included in the scope of claim 15. Focusing first on the nucleobase sequence, and for the sake of simplicity assuming the chemical backbone and internucleotide linkages are unmodified, if one limits the number of possible bases to those found in RNA, as shown in SEQ ID NO: 29, adding a single nucleobase to a 15-mer

yields 8 possible sequence combinations (A, C, G, or U added before or after the 15-mer.) [4] Adding two nucleobases yields 64 possible combinations. Adding three nucleobases yields 256 combinations. Adding 35 nucleobases to obtain a 50-mer yields 42,501,298,345,826,806,923,264 (42.5 sextillion) possible combinations. Adding 55 nucleobases to obtain an 80-mer yields 72,692,156,019,487,586,799,426,948,609,081,344 possible combinations, which is a tremendously large number of species within the scope of the claims.

193. Of course, this significantly *underestimates* the number of possible nucleobase combinations within the scope of claim 15, because claim 15 is not limited to the "natural" bases A, C, G, and U found in RNA, but also could include thymine (T), a nucleobase found in DNA, and other naturally-occurring and non-naturally occurring nucleobases such as 5-methyl-cytosine, inosine, hypoxanthine, xanthine, and many others. According to the plain language of the claim, any sequence of nucleobases may be included in the claimed AON in addition to 15 bases selected from SEQ ID NO: 29.

194. Claim 15 also allows tremendous variation in the chemical backbone and internucleotide linkages, as it requires only "a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid."

[4] Assuming only the four RNA nucleobases, the number of nucleobase combinations for a particular length AON can be calculated by this formula, where "n" equals the number of bases being added to the chain: $(4^n) \times (n+1)$. This is because each additional nucleotide can be added to either end of the SEQ ID NO: 29 sequence.

195. There is no requirement in claim 15 that the AON include one "modification" to the exclusion of the others. This is consistent with the disclosure in the AZL applications that "[h]ybrids between one or more of the equivalents among each other and/or together with nucleic acid are of course also part of the invention." (Exh. 2041 at [0019].) Nor is there any requirement in the claim that all of the nucleotides in the AON contain a modification, or the same modification if different types of modifications are present. That is, the claim includes AONs having as few as one nucleotide having a modification as recited.

196. This again leads to tremendous breadth. If one conservatively assumes that a single position in the AON contains a morpholine ring and the remaining positions could contain any of a 2'-O-Me, a 2'-O-Me-PS, a morpholine ring, a LNA, or a PNA, then the number of possible modifications to the chemical backbone is immense. For example, an 18-mer would contain 5^{17} possible chemical modifications to the backbone, or more than a hundred billion possible modifications, and a 50-mer would contain 5^{49} possible chemical modifications to the backbone. Again, however, this *underestimates* the possible number of combinations, because the claim is open to *any* possible chemical modification to the chemical backbone and internucleotide linkages provided that it contains a single modification from the recited list.

197. I have been informed that patent practitioners refer to a claim that includes a collection of individual species as a genus claim. In this case, claim 15 is directed to a genus of AONs that conservatively includes a tremendously large number of possible compounds. Claim 15 also imposes a functional requirement that the AON "induces exon 53 skipping in the human dystrophin pre-mRNA." However, the claim does not specify any conditions under which the AON induces skipping of exon 53. As I will explain below, the AZL applications do not describe a genus of AONs meeting this functional requirement, nor do they provide sufficient

information to enable a person of ordinary skill in the art to make the claimed AONs without undue experimentation.

198. Claim 76 is similar to claim 15, and generally my comments on the interpretation of claim 15 apply equally to claim 76, with some exceptions noted below:

> 76. An isolated antisense oligonucleotide of 18 to 80 nucleotides comprising at least the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre- mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1.)

199. Claim 76 differs from claim 15 in that the AON ranges in length from 18 to 80 nucleotides (compared to 15 to 80 for claim 15) and it includes the nucleobase sequence of all 18 nucleobases from SEQ ID NO: 29. The nucleobase sequence of the remaining nucleotides is undefined. Claim 76 is also exceedingly broad, as it provides tremendous variety in length, nucleobase sequence, chemical backbone, and internucleotide linkages.

200. Claim 77 depends from claim 15. It limits the AON to the exact sequence of 18 nucleotides in SEQ ID NO: 29. (Exh. 2045 at 1.) However, it is similar in scope to claim 15 in terms of the "modifications" that are permitted to the AON, and therefore conservatively encompasses more than a hundred billion possible compounds.

201. Claim 80 reads: "[t]he oligonucleotide of claim 15, wherein the oligonucleotide is complementary to exon 53 of the human dystrophin pre-mRNA." (Exh. 2045 at 2.)

202. The AZL applications broadly describe the invention as "means and methods ... for the design of appropriate complementary oligonucleotides." (Exh. 2041 at [0006].)

203. "Complementarity" refers to the relationship between two molecules. In other words, complementary molecules exhibit some degree of complementarity. The AZL

applications provide a definition for complementarity: "[t]he term complementarity is used herein to refer to a stretch of nucleic acids that can hybridise to another stretch of nucleic acids under physiological conditions. It is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the opposing strand." (Exh. 2041 at [0006].) As such, some degree of mismatching is permitted, however, the degree of mismatching permitted is not specified.

204. Based on this disclosure, in my view, the AZL applications convey to a person of ordinary skill in the art that a "complementary" AON may contain nucleobases having mismatches that do not Watson-Crick base pair with the target nucleic acid sequence.

205. In my opinion, claim 80 requires that the AON may be identical to, or have one or more mismatched bases, relative to the nucleotide sequence of exon 53, but those mismatches do not prevent the AON from hybridizing to human dystrophin pre-mRNA. Claim 80 provides no other structural limitations, including with respect to the chemical backbone and internucleotide linkages.

2. The "capable of binding" claims

206. Claims 78 and 100 define the AON in a different manner compared to claims 15 and 76. Claim 78 reads:

> 78. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O*–methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1 and 2.)

207. Claim 100 reads:

> 100. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and is capable of inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 3.)

208. Neither of these claims recites any particular nucleobase sequence that must be included within the claimed AON. Instead, claim 78 requires that the claimed AON be "capable of binding" to an undefined "exon-internal sequence" to which h53AON1 is "capable of binding." Claim 100 requires that the claimed AON be "complementary to a consecutive part of between 16 and 50 nucleotides" of an undefined "exon-internal sequence" that is "capable of binding" h53AON1.

209. Claim 78 states that the AON is "18 to 50 nucleotides in length," but no specific sequence is required to be present in the AON. Instead, the claim recites a functional requirement, that is, that the "oligonucleotide is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53."

210. The AZL applications do not provide any guidance on the meaning of "exon-internal sequence." They do explain that "[t]he skipping of an exon can be induced by the binding of antisense oligoribonucleotides (AONs) targeting either one or both of the splice sites, or exon-internal sequences." (Exh. 2041 at [0015].) Given this disclosure, although it is unclear what exactly is intended, an "exon-internal sequence" of exon 53 may be any portion of the exon that is not a splice site for the exon. But even assuming that is what "exon-internal sequence" means, there is nothing in the AZL applications informing a person of ordinary skill in the art as

to which exon-internal sequences of exon 53, that when bound by an AON, will induce skipping of the exon.

211. The ambiguity in claim 78 is compounded by a second functional clause: "and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA." (Exh. 2045 at 1 and 2.) This clause does not define the sequence or structure of the claimed AONs, but is instead informing a person of ordinary skill in the art that a specific AON, h53AON1 (SEQ ID NO: 29), is capable of binding to the same "exon-internal sequence," whatever that means, in exon 53 as is bound by the claimed AONs.

212. But it is unclear if the claimed AON needs to bind to (1) the entire portion of exon 53 bound by h53AON1, (2) an overlapping portion of exon 53 bound by h53AON1; or (3) any portion of exon 53 that is not a splice site for the exon.

213. Moreover, claim 78 does not provide any guidance concerning the conditions under which this binding is to occur. Hybridization of nucleic acids is affected by multiple factors, some of which relate to the length and composition of the nucleic acids being hybridized, and some of which relate to the conditions of the experiment, for example, ion concentration and temperature. Claim 78 is entirely silent as to any of these factors. Nor do the AZL applications provide any guidance to a person of ordinary skill in the art as to how to adjust all of the required factors to achieve the required binding. In addition, there is no disclosure in the AZL applications concerning how "binding" of the AON to the "exon-internal sequence" of the pre-mRNA is assayed or measured. The AZL applications do not disclose to a person of ordinary skill in the art how to reach a conclusion that the AON has bound, other than by reference to the separate and distinct functional requirement recited in claim that exon skipping is induced.

214. Even if claim 78 requires that the claimed AON bind all of the exon 53 nucleotides bound by h53AON1 (the narrowest possible construction), it still encompasses a genus of massive scope. Like the "comprising" claims, claim 78 encompasses AONs of 18 to 50 nucleotides, including those containing mismatches versus exon 53; natural and non-natural nucleobases; and tremendous variation in terms of the chemical backbone and internucleotide linkages. There are a tremendously large number of compounds within the scope of the genus.

215. Claim 100 is also exceedingly broad. Like claim 78, it recites an AON of "18 to 50 nucleotide in length." However, the functional requirements are slightly different: it must be (1) "complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53" and (2) "capable of inducing skipping of exon 53." (Exh. 2045 at 3.) Claim 100 further recites that h53AON1 also is "capable of binding" the exon-internal sequence of exon 53.

216. As explained above, the AZL applications do not identify the exon internal sequences within exon 53 that when bound by an AON will lead to skipping. Consequently, while defining the 18-50 nucleotide-long AON in claim 100 as being complementary to a consecutive part of 16-50 nucleotides of the "exon-internal sequence," it is unclear whether the AON needs to bind to (1) at least 16 of the 18 nucleotides of exon 53 bound by h53AON1, (2) an overlapping portion of exon 53 bound by h53AON1; or (3) any portion of exon 53 that is not a splice site for the exon. Moreover, like claim 78, claim 100 does not provide any guidance concerning the conditions under which the binding is to occur.

217. And like claim 78, claim 100 encompasses AONs of 18 to 50 nucleotides, including those containing mismatches versus exon 53; natural and non-natural nucleobases; and

tremendous variation in terms of the chemical backbone and internucleotide linkages. There are again a tremendous number of compounds potentially within the scope of the genus.

218. The additional dependent claims in the ’450 application do not meaningfully limit the scope of the claims. Claim 79 depends from claim 78, but further states that the “exon-internal sequence comprises a consecutive part of between 16 and 50 nucleotides of said exon and said oligonucleotide is complementary to said consecutive part.” (Exh. 2045 at 2.) Claim 79 does not provide any further guidance concerning the binding of h53AON1 relative to the claimed AONs, and provides no additional structural limitations concerning mismatches, natural and non-natural modified bases, chemical backbone, and internucleotide linkages.

219. Claim 82 depends from claims 15 and 100, and provides that the modification “consists of a 2’-O-methyl, 2’-O-methyl phosphorothioate.” I assume the claim has a typographical error, and was intended to say “2’-*O* –methyl or 2’-*O*-methyl-phosphorothioate.” Regardless, defining a single chemical modification does not meaningfully limit the scope of these very broad claims.[5]

220. Claim 84 depends from claims 15, 78, or 100, and recites that the single modification comprises “a morpholine ring and a phosphorodiamidate linkage.” Again, defining a single modification in a single nucleotide in the context of a massive genus of compounds,

[5] The AZL applications contain a number of such multiple dependent claims. I understand that a multiple dependent claim refers back in the alternative to more than one independent or dependent claim. I further understand that a multiple dependent claim is interpreted to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.

without even specifying where this modification occurs, does not meaningfully limit the scope of these claims.

221. Claim 86 depends from claim 84, and recites that the AON "is a morpholine phosphorodiamidate." (Exh. 2045 at 2.) Claim 86 does not address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim, explained in my analyses of claims 15, 78, and 100 above. Claims 82, 84, and 86 limit to varying degrees the chemical backbone of the claimed AONs, but do not provide any additional limitations in terms of length, nucleobase sequence, non-natural bases, or mismatches.

222. Claims 88-90, copied in full in paragraph 306 below, describe certain additional functional limitations. But they do not limit the structure of the claimed AONs in any way.

223. Claim 97 depends from claims 78 or 100, and requires that the bases of the claimed AONs "consist of DNA bases or RNA bases." (Exh. 2045 at 3.) Claim 98 depends from claims 15, 76, 77, 78, or 100, and recites that the oligonucleotide consists of "RNA." (Exh. 2045 at 3.) I assume that "RNA" is a typographical error and should say "RNA bases." I understand that because these claims are limited to natural bases. Claims 78 and 100 must include nucleobases in addition to the natural bases found in DNA and RNA. The number of non-natural bases is large, and neither the claims nor the specification provide any guidance as to which non-natural bases, if any, will be able to meet the various functional limitations of claims 78 and 100. Further, the lack of such guidance creates an open question to a person of ordinary skill in the art as to the identity of non-natural bases that are "capable of binding" (claim 78), "complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53" (claim 100) and capable of "inducing skipping of exon 53" (claims 78 and 100) – a question for which neither the claims nor the specification provides an answer.

224. In any case, these claims do not meaningfully reduce claim scope because they do not prevent mismatches, define the structure of the chemical backbone, or define the structure of the internucleotide linkages. Moreover, they do not resolve the "capable of binding" issues addressed above.

225. Claim 101 depends from claims 15, 76, 77, 78, 97, or 100, and requires that the AON is "less than 50 nucleotides in length." (Exh. 2045 at 3.) Claim 102 depends from claims 15, 76, or 77, and requires that the AON is "less than 80 nucleotides in length." (Exh. 2045 at 3.) These claims do not provide any other structural limitations, and are still of exceedingly broad scope.

226. Claim 103 recites: "[t]he oligonucleotide of claim 78 or 100, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence." (Exh. 2045 at 4.) Claim 103 does not provide any further guidance concerning the binding of h53AON1 relative to the claimed AONs, and provides no additional structural limitations concerning non-natural bases, chemical backbone, and internucleotide linkages.

B. Interpretation of the Claims in the '210 Application

227. The claims of the '210 application are also exceedingly broad. In general, all of these claims are directed to AONs that are "capable of binding" to an exon-internal sequence of exon 51 and inducing skipping of that exon.

228. Claims 11, 15, 19, and 26 are independent claims, all of which have similar language:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a morpholine ring, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

> 15. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a peptide nucleic acid and/or locked nucleic acid, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.
>
> 19. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a 2'-*O*-methyl ribose moiety, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.
>
> 26. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a modification which confers increased resistance to RNAseH, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon internal sequence.

(Exh. 2047 at 1-3.)

229. The terms of these claims are all essentially the same except for the recited chemical modifications. Claim 11 requires "a" morpholine ring; claim 15 requires "a" PNA or LNA; claim 19 requires "a" 2'-*O*-methyl ribose moiety; and claim 26 requires "a" modification that confers increased resistance to RNAseH.

230. But all of these claims are directed to isolated AONs that are 20 to 50 nucleotides in length. All of these claims define the AONs functionally in a manner analogous to that described above for claim 78 of the '495 application, except that the claims are directed to exon 51 instead of exon 53 and therefore recite an exon 51 AON, h51AON1, instead of h53AON1. Accordingly, as addressed in paragraphs 209-214 above, these claims all encompass a tremendous number of possible candidates, and also suffer from the same interpretation challenges with respect to the "exon-internal sequence."

231. It is unclear whether these claims require that the claimed AONs bind to (1) the entire portion of exon 51 bound by h51AON1, (2) an overlapping portion of exon 51 bound by h53AON1; or (3) any portion of exon 51 that is not a splice site for the exon. Moreover, these claims do not provide any guidance concerning the conditions under which this binding is to occur. *See* paragraphs 211-213 above discussing '495 application 78.

232. Even if these claims require that the claimed AON bind all of the exon 51 nucleobases bound by h51AON1 (the narrowest possible construction), they still are directed to a genus of massive scope. These claims encompass AONs of 20 to 50 nucleotides, including those containing mismatches versus exon 51; natural and non-natural nucleobases; and tremendous variation in terms of the chemical backbone and internucleotide linkages. As I explained in paragraphs 192 and 193, each of these claims potentially encompasses a tremendously large number of different chemical compounds.

233. The dependent claims do not meaningfully restrict the scope of these independent claims.

234. Claim 12 of the '210 application reads: "[t]he oligonucleotide of claim 11, 15, 19, or 26, said exon-internal sequence comprising a consecutive part of between 16 and 50 nucleotides of said exon and wherein said oligonucleotide is complementary to said consecutive part." (Exh. 2047 at 1.) Claim 12 does not provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs, and provides no additional structural limitations concerning mismatches, natural and non-natural modified bases, chemical backbone, and internucleotide linkages.

235. Claim 14 depends from claim 11, and requires that the AON further comprise "a" phosphorodiamidate linkage. Defining a single chemical modification does not meaningfully limit the scope of these very broad claims.

236. Claim 17 depends from claim 15, and recites that "each linkage" is a phosphorodiamidate internucleoside linkage." Based on my experience, I find this claim confusing because PNAs contain peptide bond internucleoside linkages and LNAs typically contain phosphorothioate internucleoside linkages. Claim 18 depends from claims 11 or 17, and recites that the AON is "a morpholino phosphorodiamidate." These claims do not address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim, explained in my analyses of the independent claims above. Claim 18 is also inconsistent, in that it requires the claimed AON to be a "morpholino" but through its dependency from claim 15 it must also comprise a PNA and/or an LNA.

237. Claim 20 recites that the AON further comprise "a" phosphorothioate internucleoside linkage. Claim 21 recites that each linkage is a "phosphorothioate linkage." Claim 22 recites that each AON is a "2'-O-methyl phosphorothioate" AON. None of these claims address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim, explained in my analysis of the independent claims above. Nor do they provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs.

238. Claims 23, 24, and 25 recite certain additional functional limitations. But they do not limit the structure of the claimed AONs in any way.

239. Claim 27 depends from claims 11, 15, 19, or 26, and requires that the bases of the claimed AON "consist of DNA bases or RNA bases." Claim 27 does not reduce claim scope

because it does not prevent mismatches, define the structure of the chemical backbone, define the structure of the internucleotide linkages, or meaningfully reduce the number of possible nucleobase combinations. Moreover, claim 27 does not resolve the "capable of binding" issues addressed above. In addition, my comments in paragraph 223 concerning the impact of claim 97 and 98 of the '495 application on the scope of the independent claims also apply here as claim 27 raises the same issues for claims 11, 15, 19, and 26.

240. Claim 28 also depends from claims 11, 15, 19, or 26, but requires that the AON be "less than 50 nucleotides in length." This claim does not provide any other structural limitations, and is still of exceedingly broad scope.

241. Claim 29 of the '210 application reads: "[t]he oligonucleotide of claim 11, 15, 19 or 26, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence." (Exh. 2047 at 3.) Claim 29 does not provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs, and provides no additional structural limitations concerning non-natural bases, chemical backbone, and internucleotide linkages.

C. Interpretation of the Claims in the '992 Application

242. The claims of the '992 application are also exceedingly broad. In general, these claims are directed to methods of using AONs that are "capable of binding" to an exon-internal sequence of exon 51 and inducing skipping of that exon.

243. Claims 1 and 2 are the only independent claims in the '992 application. They recite as follows:

> 1. A method for inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 20 to 50 nucleotides in length to a cell, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1

(UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

2. A method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a patient by inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 20 to 50 nucleotides in length to a cell of said patient, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

(Exh. 2050 at 1.)

244. Claim 1 is directed to a method for "inducing skipping." Claim 2 is directed to a method for "treating" DMD or BMD "in a patient." Although the '992 application claims are directed to methods, the language in the claims that is used to define the AONs used in the methods is the same as the language in the '210 application claims. Thus, both claims are directed to isolated AONs that are 20-50 nucleotides in length, wherein the claimed AONs are "capable of binding" to an "exon-internal sequence" that h51AON1 is also "capable of binding."

245. These claims consequently also cover a tremendous number of possible AONs. *See* paragraphs 206-217 and 228-232 above. Because the claims in the '992 application parallel the language used in the '210 application, my views concerning the proper interpretation of the '210 application claims apply equally to the '992 application claims.

246. Briefly, independent claims 1 and 2 encompass a tremendous number of AONs. It is unclear whether these claims require that the claimed AONs bind to (1) the entire portion of exon 51 bound by h51AON1, (2) an overlapping portion of exon 51 bound by h51AON1; or (3) any portion of exon 51 that is not a splice site for the exon. Moreover, these claims do not provide any guidance concerning the conditions under which this binding is to occur.

247. Even if one requires that the claimed AONs bind the entire sequence of nucleotides of exon 51 bound by h51AON1 (the narrowest possible construction), they still are

directed to a genus of massive scope. These claims encompass AONs of 20 to 50 nucleotides, including those containing mismatches versus exon 51; natural and non-natural nucleobases; and tremendous variation in terms of the chemical backbone and internucleotide linkages. Each of these claims potentially encompasses methods of using a tremendously large number of different chemical compounds.

248. The dependent claims do not meaningfully restrict the scope of the independent claims.

249. Claims 3, 4, and 5 depend from claim 1, but do not provide any additional structural limitations for the claimed AONs.

250. Claim 6 depends from claim 1 and recites that the AON "comprises DNA." Claim 7 depends from claim 1 and recites that the AON "comprises RNA." Because unmodified DNA and RNA AONs are rapidly degraded, these unmodified AONs are unlikely to work for exon skipping. In any case, these claims do not provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs, and do not address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim.

251. Claim 10 depends from claim 1 and requires that the AON comprise "a modification." Claims 11-18 all address possible modifications to the chemical backbone or internucleotide linkages. But none of these claims address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim, explained in my analysis of the independent claims above. Nor do they provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs.

252. Claims 19-21 depend from claim 1 and recite certain additional functional limitations. But they do not limit the structure of the claimed AONs in any way.

253. Claim 22 depends from claim 1, and recites that the exon internal sequence comprises "a consecutive part of between 16 and 50 nucleotides of said exon and wherein said oligonucleotide is complementary to said consecutive part." Claim 22 does not provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs. Claim 22 also provides no additional structural limitations concerning non-natural bases, mismatches, chemical backbone, and internucleotide linkages.

254. Claim 23 depends from claim 1 and recites that the AON is capable of binding "without mismatches" to the exon-internal sequence. Claim 23 does not provide any further guidance concerning the binding of h51AON1 relative to the claimed AONs, and provides no additional structural limitations concerning non-natural bases, chemical backbone, and internucleotide linkages.

255. Claim 24 depends from claim 1 and recites that the AON consists of DNA bases or RNA bases. I interpret this to mean that AON of claim 24 includes only the natural DNA bases (that is, A, C, G, and T) or only the natural RNA bases (that is, A, C, G, and U). I understand that because claim 24 is limited to AONs consisting of these natural bases, claim 1 must cover AONs that may include natural and non-natural modified bases. Claim 24 does not significantly reduce claim scope because it does not prevent mismatches, define the structure of the chemical backbone, define the structure of the internucleotide linkages, or meaningfully reduce the number of possible nucleobase combinations. Moreover, claim 24 does not resolve the "capable of binding" issues addressed above.

256. Claim 25 depends from claim 1 and recites that the AON is "less than 50 nucleotides in length." This claim does not provide any other structural limitations, and is still of exceedingly broad scope.

257. Claim 26 depends from claim 1 and recites that the AON "comprises a modification which confers increased resistance to an endonuclease." Claim 27 depends from claim 26 and requires that the endonuclease be "RNAse H." These are additional functional limitations, but the claims do not further limit the structure of the claimed AONs in any way.

D. Interpretation of the Claims in the '279 Application

258. The claims in the '279 application are very similar to the claims of the '992 application. Whereas the '992 application claims are for methods that involve skipping of exon 51, the '279 application claims are directed to methods involving skipping of exon 53. And like the '992 claims, the '279 claims are exceedingly broad.

259. Claims 1 and 2 are independent claims. They recite as follows:

> 1. A method for inducing the skipping of exon 53 of the human dystrophin pre-mRNA in a subject with Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD), or a cell derived from the subject, said method comprising providing an oligonucleotide of 15 to 50 nucleotides in length to said subject or said cell, wherein said oligonucleotide sequence is capable of binding to an exon internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, wherein said oligonucleotide induces skipping of said exon in the subject or the cell and wherein mRNA produced from skipping exon 53 of the dystrophin pre-mRNA encodes a functional dystrophin protein or a dystrophin protein of a Becker subject.
>
> 2. A method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a subject by inducing the skipping of exon 53 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 15 to 50 nucleotides in length, said oligonucleotide sequence is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and, wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon internal sequence of exon 53 pre-mRNA, and wherein said oligonucleotide induces skipping of said exon in the subject.

(Exh. 2053 at 2.)

260. Claim 1 is directed to a method for "inducing skipping." Claim 2 is directed to a method for "treating" DMD or BMD "in a patient." Although the '279 application claims are directed to methods, the language in the claims that is used to define the AONs used in the methods is essentially the same as the language in '495 application claim 78. Thus, both claims are directed to isolated AONs that are 15-50 nucleotides in length (in '495 application claim 78 the AON is "18 to 50 nucleotides in length), wherein the claimed AONS are "capable of binding" to an "exon-internal sequence" that h53AON1 is also "capable of binding."

261. Consequently, these claims cover a tremendous number of possible AONs. Because the claims in the '279 application parallel the language used in '495 application claim 78, my view concerning the proper interpretation of claim 78 applies equally to the '279 application claims. *See* paragraphs 206-217 above.

262. Briefly, independent claims 1 and 2 encompass a tremendous number of AONs. It is unclear whether these claims require that the claimed AONs bind to (1) the entire portion of exon 53 bound by h53AON1, (2) an overlapping portion of exon 53 bound by h53AON1; or (3) any portion of exon 53 that is not a splice site for the exon. Moreover, these claims do not provide any guidance concerning the conditions under which this binding is to occur.

263. Even if one requires that the claimed AONs bind the entire portion of exon 53 bound by h53AON1 (the narrowest possible construction), they still are directed to a genus of massive scope. These claims encompass AONs of 15 to 50 nucleotides, including those containing mismatches versus exon 53; natural and non-natural nucleobases; and tremendous variation in terms of the chemical backbone and internucleotide linkages. Each of these claims potentially encompasses methods of using a tremendously large number of different chemical compounds.

264. The dependent claims do not meaningfully restrict the scope of the independent claims.

265. Claim 3 depends from claim 1 and limits the cell to a muscle cell. (Exh. 2053 at 2.) This does not narrow the scope of the claim at all in terms of the genus of AONs that may be used in the method.

266. Claim 4 depends from claim 1 and requires that the AON "comprises a modification." (Exh. 2053 at 2.) Claims 5-10 refer to specific chemical modifications. (Exh. 2053 at 3.) None of these claims address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim, explained above in my analysis of the independent claims. Nor do they provide any further guidance concerning the binding of h53AON1 relative to the claimed AONs.

267. Claim 11 depends from claim 1 and limits the AON to "DNA bases or RNA bases." (Exh. 2053 at 3.) I interpret this to mean that the AON of claim 11 includes only the natural DNA bases (that is, A, C, G, and T) or only the natural RNA bases (that is, A, C, G, and U). I understand that because claim 11 is limited to AONs consisting of these natural bases, claim 1 must cover AONs that may include non-natural bases. Claim 11 does not significantly reduce claim scope because it does not prevent mismatches, define the structure of the chemical backbone, define the structure of the internucleotide linkages, or meaningfully reduce the number of possible nucleobase combinations. Moreover, claim 11 does not resolve the "capable of binding" issues addressed above.

268. Claims 12-14 depend from claim 1 and recite certain additional functional limitations. (Exh. 2053 at 3.) But they do not limit the structure of the claimed AONs in any way.

269. Claims 15 and 16 depend from claims 1 and 2, respectively, and require that the AON "is less than 50 nucleotides." (Exh. 2053 at 3 and 4.) These claims do not provide any other structural limitations, and are still exceedingly broad in scope.

270. Claims 20 and 21 are for an expression vector (claims 20) or a gene delivery vehicle comprising the expression vector (claim 21). (Exh. 2053 at 4.) The language describing the AON in these claims is the same as the description in claim 1. Accordingly, these claims are tremendously broad.

271. Claim 22 depends from claim 1 and states that the AON "is 18 nucleotides and comprises the base sequence of the sequence CUGUUGCCUCCGGUUCUG (SEQ ID NO: 29)." (Exh. 2053 at 4.) Although limited to the exact sequence of SEQ ID NO: 29, the AONs used in the method of claim 22 may include any of the possible modifications recited in claims 4-10. Consequently, the AONs of claim 22 cover a tremendous number of compounds.

272. Claim 23 recites: "[t]he method of claim 1, wherein said exon-internal sequence comprises a consecutive part of between 16 and 50 nucleotides of said exon and said oligonucleotide is complementary to said consecutive part." (Exh. 2053 at 4.) Claim 23 does not provide any further guidance concerning the binding of h53AON1 relative to the claimed AONs. Claim 23 also provides no additional structural limitations concerning non-natural bases, mismatches, chemical backbone, and internucleotide linkages.

273. Claim 24 depends from claim 1 and requires that the AON "consist of DNA bases or consist of RNA bases." (Exh. 2053 at 4.) Claim 25 also depends from claim 1, and requires that the AON consists of RNA bases. (Exh. 2053 at 4.) Because unmodified DNA and RNA AONs are rapidly degraded, if unmodified the AONs are unlikely to work for exon skipping. In any case, these claims do not provide any further guidance concerning the binding of h53AON1

relative to the claimed AONs, and do not address the tremendous number of possible nucleobase sequence combinations included within the scope of the claim.

274. Claim 26 depends from claim 1 and states that the AON "is capable of binding without mismatches to said exon-internal sequence." (Exh. 2053 at 4.) Claim 26 does not does not provide any further guidance concerning the binding of h53AON1 relative to the claimed AONs, and provides no additional structural limitations concerning non-natural bases, chemical backbone, and internucleotide linkages.

VII. WRITTEN DESCRIPTION

A. Legal Standard

275. I have been informed that there is a written description requirement for patentability. It is my understanding that to meet the written description requirement a patent application must reasonably convey to one of ordinary skill in the art that the applicant had possession of the full scope of the claims in the application at the time the application was filed. I have also been informed that the level of detail required in a patent application to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.

276. I have also been informed that the written description requirement for a claimed genus may be met in two ways. First, the requirement may be met by the disclosure in the patent application of a sufficient number of species representative of the entire genus. Second, the written description requirement may be met by disclosure in the patent application of relevant identifying characteristics, that is, structure or other physical and/or chemical properties, which are correlated to the function possessed by the members of the genus sufficient to distinguish the claimed genus.

277. Applying this understanding, in my opinion, the AZL applications do not provide written description support for the full scope of the claims in the '495, '210, '992, and '279 applications.

B. The Claims in the '495 Application

278. The claims in the '495 application are directed to AONs that induce skipping of exon 53. (Exh. 2045 at 1-3.) The AZL applications disclose two species of AON (h53AON1 and h53AON2) that bind to exon 53. But only h53AON1, which has "a full-length phosphorothioate backbone and 2'-*O*-methyl modified ribose molecules" (Exh. 2041 at [0047]) and consists of nucleobases A, U, C, and G, is reported to induce exon skipping. (Exh. 2041 at Table 2.) The other AON, h53AON2, was also 18 nucleotides in length, also contained a 2'-O-Me-PS backbone, and also contained exclusively the natural nucleobases A, C, G, and U—yet failed to induce skipping of exon 53. (Exh. 2041 at 15.) No explanation is offered for this failure. So the AZL applications describe only one species of AON that is capable of inducing skipping of exon 53, at least *in vitro*. But the claims are much, much broader than this narrow disclosure of a single species.

279. Claims 15 reads as follows:

> 15. An isolated antisense oligonucleotide of 15 to 80 nucleotides comprising at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-, phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1.)

280. I have provided my views on how a person of ordinary skill in the art would interpret claim 15 in paragraphs 191-197 of this declaration. The claim covers a tremendously large genus of structurally and chemically different AONs. Yet all of the AONs must perform

the same function of inducing exon 53 skipping. The '495 application does not describe the full range of AONs that are embraced by this genus. As explained below, the one species of AON (h53AON1) that is described in the '495 application is not representative of all AONs of 15 to 80 nucleotides comprising 15 bases of SEQ ID NO: 29 and capable of inducing exon skipping. Given the unpredictability of this technology (see, for example, paragraphs 68-81), a person of ordinary skill in the art could not predict from h53AON1 the operability of any other AONs having nucleotide sequences that differ from h53AON1. That is, the '495 application does not describe any relevant identifying structural or chemical features that correlate with the required function of inducing exon 53 skipping in human dystrophin pre-mRNA.

281. The sole described species of AON is 18 nucleotides long, having the sequence cuguugccuccgguucug, a full length phosphorothioate backbone, and 2'-*O*-methyl modified ribose molecules. (Exh. 2041 at Table 2 and [0047].) Having reviewed the AZL applications, I did not find any other species of AON described that falls within the scope of claim 15. There are no morpholinos, no LNAs, no PNAs, and no hybrids disclosed. There are no phosphorodiamidate internucleotide linkages disclosed. There are no AONs with non-natural bases disclosed. There are no AONs longer than 18 nucleotides disclosed. There are no AONs disclosed that contain thymine in place of uracil.

282. I understand that disclosure of a single species within a genus does not entitle one to a patent on the genus when the technology involved is unpredictable. In my opinion, as discussed above in section IV.E.3, using AONs to induce exon skipping was a very unpredictable technology in March of 2003, and it remains so to this day.

283. Evidence of that unpredictability is found within the AZL applications. The AZL applicants used their rationale for designing exon skipping AONs to design two AONs that

would induce skipping of exon 53. As shown in Table 2, only one of those two AONs worked. (Exh. 2041 at Table 2.) The AZL applications make no attempt to explain why one AON was purportedly successful in inducing skipping, while the other was a failure.

284. Looking at the AONs included in Table 2 provides a better understanding of just how unpredictable this technology is. For example, the two AONs designed to induce skipping of exon 2 have over lapping nucleotide sequences:

```
h2AON1                    cccauuuugugaauguuuucuuuu
h2AON2          uugugcauuuacccauuuugug
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Despite that overlap, h2AON1 purportedly induced skipping, while h2AON2 did not. (Exh. 2041 at Table 2.)

285. And yet for another pair of overlapping AONs, both members of the pair did purportedly induce skipping:

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h29AON1               uauccucugaaugucgcauc
h29AON2          gguuauccucugaaugucgc
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286. There is no explanation in the AZL applications for these disparate results.

287. Much of the data in Table 2 was published in 2002 by the AZL investigators. (Exh. 2010 at S73 and Table 2.) The authors provided the following observations on their experimental results:

> Of the 30 AONs tested, as many as 20 induced specific exon skipping. **There was no significant correlation between length or sequence content of the AON and its effectiveness (see Table 1). We hypothesize that in most cases the mere accessibility of the targeted RNA region, and thus the capability of the AONs to bind, determines their efficacy**.... To predict the secondary structure of the targeted pre-mRNA regions, we have used the RNA mfold version 3.1 server [22]. Although this analysis hints at the most favorable local structure which may help in the design of AONs, it is not capable of predicting the overall complex structure of the entire DMD pre-mRNA. **We therefore have no insight into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore have to be tested empirically in the cells, as was done in this study**.

(Exh. 2010 at S76; emphasis added.)

288. Given these conclusions on the state of the art in 2002, it is unsurprising that these investigators reported in 2001 that "[t]he efficacy of AONs is largely determined by their binding affinity for the target sequence. Due to base composition and pre-mRNA secondary or tertiary structure, ***it is difficult to predict which AONs are capable of binding the target sequence***." (Exh. 2012 at 1548; emphasis added.)

289. Similar examples were reported by the AZL investigators in a 2005 publication (Exh. 2016), that is, years after the effective filing date of the AZL applications. The same design rationale described in the AZL applications was applied in the publication. (Exh. 2016 at 285, first and second columns.) Table 1 in the publication provides the sequences of the AONs and whether or not they induced skipping. The following pairs of AONs are found in the Table (+ and – refer to skipping ability):

h29AON10	guaguucccuccaacg	-
h29AON11	cauguaguucccucc	+
h43AON2	uuguuaacuuuuucccauu[6]	+
h43AON3	uguuaacuuuuucccauugg	-
h46AON8	gcuuuucuuuuaguugcugc	++
h46AON9	uuaguugcugcucuu	-
h48AON3	ggucuuuuauuugagcuuc	-

[6] There is a discrepancy between the disclosure of AZL's 2005 publication and the sequence as shown in the application as filed. In the 2005 publication, the sequence is shown as uuguuaacuuuuuccauu, while in Table 2 of the AZL applications it shown as above having a sequence of ccc toward the 3' end of the AON. I have assumed the latter is correct as it corresponds to the sequence of h43AON3.

h48AON7	uuuauuugagcuucaaauuu	+

290. It is evident from these results that applying the AON design rationale described in the AZL patents is a hit or miss proposition in terms of whether any given AON will be capable of inducing skipping, even in situations where the AONs are very similar to each other in terms of nucleotide sequence and other variables concerning the chemical backbone are fixed. All of the AONs described in the study "contain 2'-O-methyl RNA and full-length phosphorothioate (PS) backbones." (Exh. 2016 at 285.) None of the AONs disclosed were longer than 24 nucleotides and the majority of the AONs were 20 nucleotides in length or shorter. (Exh. 2016 at Table 1.) None of those AONs include non-natural bases. Given the common chemical modifications of these AONs, the data reported in this paper demonstrates the unpredictable impact that length and nucleotide composition makes with respect to efficiency in inducing exon skipping.

291. This recognition of the lack of predictability continued beyond 2005. A 2007 paper co-authored by several members of the AZL group states that "several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], ***there are still no clear rules to guide investigators in their design***, and in mouse and human muscle cells *in vitro* ***there is great variability for different targets and exons***." (Exh. 2013 at 807; emphasis added.)

292. And again in 2009 the AZL investigators wrote that while existing software programs can facilitate design, "in general ***a trial and error procedure*** is still involved to identify potent AONs." (Exh. 2014 at 548.)

293. Finally, as I mentioned in paragraphs 73-77, studies performed before, and long after, the filing date of the AZL applications demonstrated that small changes in nucleotide

sequences in overlapping AONs can convert an AON from one that induces skipping to one that does not.

294. Given all of these publications and their data, from the AZL investigators and others working in the field, designing AONs capable of inducing exon skipping was highly unpredictable as of the filing date of the AZL applications.

295. In view of this lack of predictability, in my opinion, the one species (h53AON1) disclosed in the ’495 application is not representative of the entire genus of AONs defined by claim 15.

296. The ’495 application also fails to describe a structural feature that is common to all of the members of the genus that correlates with the required function of inducing skipping of exon 53 in the human dystrophin pre-mRNA. The only common structural feature among members of the genus of claim 15 is that they contain “at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29).” (Exh. 2045 at 1.) But there is no data in the AZL applications showing that AONs containing 15 bases of that sequence will induce skipping. Indeed, the AZL applications do not provide any data for such AONs. And given the unpredictability inherent in this technology, a person of ordinary skill would need to empirically test each and every AON to determine whether it would be capable of inducing skipping.

297. The unpredictability is magnified as the length of the AON extends beyond the 18 nucleotide sequence of SEQ ID NO: 29. As a person of ordinary skill in the art would have understood, small changes in length and composition of the AON can convert a skipping-inducing AON into one that will no longer induce skipping. I note that the longest AON reported in the ’495 application is only 24 nucleotides long. (Exh. 2041 Table 2.) This doesn’t come close to the 80-mers permitted within the genus of claim 15. And there is no way to

predict which additions of nucleotides to SEQ ID NO: 29 will maintain its ability to induce skipping, and which additions will cause it to be lost. That uncertainty, coupled with the tremendous size of the claimed genus, in my opinion, would clearly leave a person of ordinary skill guessing as to what common feature or features all of the members of the genus would need to possess in order to be functional.

298. In summary, due to the unpredictability in this technology, the broad scope of the claimed genus, and the disclosure in the '495 application of just a single member of the genus, a person of ordinary skill in the art would conclude from the application that the applicants did not have possession of the claimed genus.

299. Claim 77 reads: "[t]he oligonucleotide of claim 15, wherein the oligonucleotide is 18 nucleotides and comprises the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA." (Exh. 2045 at 1.) Although claim 77 is limited to a single nucleotide sequence, it encompasses AONs with modifications to the chemical backbone and modifications to the internucleotide linkages. If we conservatively assume that one position in the AON contains a morpholine ring and the remaining 17 nucleotides are modified, they could contain a 2'-O-Me, a 2'-O-Me-PS, a morpholine ring, a LNA, or a PNA, that means claim 77 encompasses 5^{17} possible chemical combinations, or more than a hundred billion possible compounds.

300. The AZL applications are directed to AONs and methods of using them for human clinical indications. (Exh. 2041 at [0002].) Consequently, at a minimum, the claimed AONs must be capable of inducing exon skipping within human cells. (Exh. 2041 at [0026].) Given the variability in the chemistry permitted by claim 77, not all of the members of the genus will be capable of inducing skipping within a cell. For example, claim 77 includes a large

number of AONs that are minimally modified, such as those that contain a morpholine ring, a PNA, an LNA, or a phosphorodiamidate linkage. Such AONs would be subject to degradation within the intracellular environment.

301. For this reason, the '495 application does not disclose a common structural feature of the genus of AONs within claim 77 that will permit the AONs to achieve their required function. And only one species within this genus (h53AON1) is described. Given this scant disclosure, the '495 application does not convey possession of the genus of AONs encompassed by claim 77.

302. Claim 80 reads: "[t]he oligonucleotide of claim 15, wherein the oligonucleotide is complementary to exon 53 of the human dystrophin pre-mRNA." (Exh. 2045 at 2.) Although the genus of claim 80 is theoretically narrower than the genus of claim 15, the '495 application also fails to convey possession of this genus of AONs. Only a single species (h53AON1) within the genus is disclosed. And while the genus of AONs recited by claim 80 is complementary to exon 53 of the human dystrophin pre-mRNA, the genus still embraces a considerable number of species given (1) the 15 to 80 nucleotide length range permitted; (2) the ability to have mismatched bases in the AON while remaining "complementary" to exon 53 (see paragraph 137); and (3) the tremendous variety of backbone chemistries encompassed by the claim, as indicated in my discussion of claim 77 above.

303. Again, there is no description of a common structural feature possessed by the members of the genus that permits the AONs to induce skipping of exon 53. The unpredictability in the art means that a person of ordinary skill cannot envision which AONs within the genus will induce skipping, and which will not. Empirical testing is required.

Consequently, the '495 application does not show possession of the genus of AONs recited by claim 80.

304. Claim 82 reads: "[t]he oligonucleotide of claim 15 or 100, wherein said modification consists of a 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate." (Exh. 2045 at 2.) I assume the claim has a typographical error, and was intended to say "2'-*O* –methyl or 2'-*O*-methyl-phosphorothioate." Regardless, limiting the modification to either of those two chemistries does not address the lack of description for the immense number of possible nucleobase combinations included within the scope of the claim, similar to my analysis of claim 15 above. Also, in requiring only "a" single modification in a claim that encompasses hybrid AONs, claim 82 does not meaningfully limit the tremendous variety of backbone and internucleotide chemistries included within its scope. In my opinion, the full scope of the subject matter of claim 82 is not described in the '495 application.

305. Claims 84 and 86 also limit the scope of the modifications in the AON. In claim 84, which depends from claims 15, 78, or 100, "said modification compris[es] a morpholine ring and a phosphorodiamidate linkage." (Exh. 2045 at 2.) Claim 86 depends from claim 84, and requires that the AON "is a morpholine phosphorodiamidate oligonucleotide." (Exh. 2045 at 2.) Neither of these limitations on the AON chemistry addresses the lack of description for the tremendous number of possible combinations included within the scope of the claim, similar to my analysis of claim 15 above. In my opinion, the full scope of the subject matter of claims 84 and 86 is not described in the '495 application.

306. Claims 88, 89, and 90 read as follows:

> 88. The oligonucleotide of claim 15, 78, or 100, wherein the oligonucleotide induces exon 53 skipping of the human dystrophin pre-mRNA and dystrophin expression at the muscle cell upon transfection of primary human muscle cells with at least 100 nM of said oligonucleotide and incubation for at least 16 hours.

89. The antisense oligonucleotide of claim 88, wherein exon 53 skipping is detected by RT-PCR and/or sequence analysis.

90. The oligonucleotide of claim 88, wherein dystrophin expression at the muscle cell is detected by immunohistochemical and/or western blot analysis.

(Exh. 2045 at 2 and 3.)

307. I note that there is no mention in claims 15, 78, or 100 of the "the muscle cell" that is referred to in claim 88. Regardless, claim 88 is directed to conditions for conducting skipping of exon 53. Claims 89 and 90, although referring to the AON, add general requirements relating to how exon skipping is detected, and not requirements on the AON *per se*. None of the requirements of claims 88-90 address the bases for the lack of description which I have identified that exist for claim 15. In my opinion, the full scope of claims 88-90 is not described in the '495 application.

308. Claim 98 reads: "[t]he oligonucleotide of claim 15, 76, 77, 78, or 100, said oligonucleotide consisting of RNA." (Exh. 2045 at 3.) Requiring that the AON consist of RNA does not narrow the scope of the genus of AONs within claim 15 in terms of the sequence of nucleotides present in species of AONs within the genus. In my opinion, the full scope of claim 98 is not described by the '495 application.

309. Claim 101 reads: "[t]he oligonucleotide of claim 15, 76, 77, 78, 97 or 100, said oligonucleotide being less than 50 nucleotides in length." (Exh. 2045 at 3.) Claim 102 is similar: "[t]he oligonucleotide of claim 15, 76, or 77, said oligonucleotide being less than 80 nucleotides in length." (Exh. 2045 at 3.) Neither of these claims has a significant impact on the scope of claim 77, because in claim 77 "the oligonucleotide is 18 nucleotides" and so necessarily is less than 50 (or 80) nucleotides in length. Claim 102 excludes AONs of 80 nucleotides from the genus, leaving within the genus AONs ranging in size from 15 to 79 (claim 15), or 18 to 79 (claim 76), nucleotides. Similarly, limiting AONs within the scope of the independent claims,

per claim 101, still leaves the claims covering a large genus of AONs that are not fully described. In my opinion, the '495 application does not provide a description of the full scope of AONs for claims 101 and 102.

310. Claim 76 reads as follows:

> 76. An isolated antisense oligonucleotide of 18 to 80 nucleotides comprising at least the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre- mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1.)

311. I have provided my views on how a person of ordinary skill in the art would interpret claim 76 in paragraphs 198 and 199 of this declaration.

312. In my opinion, the '495 application fails to provide a description of the genus of AONs recited by claim 76 for the same reasons it fails to provide a description of the genus recited by claim 15.

313. The AON represented by SEQ ID NO: 29 is the only disclosed species within the broad genus of AONs encompassed by claim 76. I understand that a single species cannot be representative of a genus, particularly in a situation such as here for claim 76 where the genus is so tremendously large.

314. And for the reasons I have just explained for claim 15, the '495 application does not describe a common structural feature correlating to the functional requirement common to the members of the claim 76 genus of inducing skipping of exon 53. In my opinion, a person of ordinary skill in the art would conclude that the '495 application does not convey the applicants had possession of the genus of AONs embraced by claim 76.

315. Claim 78 reads as follows:

> 78. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O*–methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1 and 2.)

316. I have provided my views on how a person of ordinary skill in the art would interpret claim 78 in paragraphs 208-214 of this declaration.

317. Again, only one species (h53AON1) of this incredibly broad genus is disclosed in the '495 application. In my opinion, that one species is not representative of the members of the genus for the reason I have discussed with respect to claims 15 and 76.

318. The '495 application also fails to describe a structural feature that is common to the member of this genus, and which correlates with the functional requirement of inducing exon 53 skipping. Given the "capable of binding" language that appears twice in claim 78, the claim, in my view, embraces a larger genus of AONs than embraced by claims 15 and 76. But as in the case of those claims, no common structural feature of species within the genus is disclosed. Without that disclosure, and lacking disclosure of a representative number of species within the genus, the '495 application does not convey possession of the subject matter of claim 78.

319. Claim 79 reads: "[t]he oligonucleotide of claim 78, wherein said exon-internal sequence comprises a consecutive part of between 16 and 50 nucleotides of said exon and said oligonucleotide is complementary to said consecutive part." (Exh. 2045 at 2.) Despite this additional limitation, the '495 application also fails to convey possession of this genus of AONs. Only a single species (h53AON1) within the genus is disclosed. And while the genus of AONs recited by claim 79 is complementary to a consecutive part of between 16 and 50 nucleotides of

an exon-internal sequence of 53 of the human dystrophin pre-mRNA, the genus still embraces a considerable number of species given (1) the 16 to 50 nucleotide length range permitted, (2) the ability to have mismatched bases in the AON while remaining complementary to exon 53, and (3) the ability to have modifications to the chemical backbone and/or internucleotide linkages.

320. Although the genus is more narrow, in my opinion, there is no description of a common structural feature possessed by the members of the genus of claim 79 that permits the AONs to induce skipping of exon 53. The unpredictability in the art means that a person of ordinary skill cannot envision which AONs within the genus will induce skipping, and which will not. Consequently, the '495 application does not show possession of the genus of AONs recited by claim 79.

321. Claim 97 reads: "[t]he oligonucleotide of claim 78 or 100, wherein the bases of said nucleotides of said oligonucleotide consist of DNA bases or consists of RNA bases." (Exh. 2045 at 3.) Limiting the nucleotides of the AONs to DNA bases or RNA bases does not address the deficiencies with respect to the scope of the description that I have identified for claim 78. In my opinion, the full scope of claim 97 is not described by the '495 application.

322. Claim 103 reads: "[t]he oligonucleotide of claim 78 or 100, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence." (Exh. 2045 at 4.) Although this narrows the scope of the genus relative to the genus of claims 78 or 100, the genus is still very large, and the '495 application only discloses one species that purportedly falls within it. And as I have explained, the unpredictability of this technology means that there is no way to know, *a priori*, whether or not any AONs extending up to 50 nucleotides in length, even if they are capable of binding without mismatches to an exon-internal sequence, will retain the capacity to induce skipping. Consequently, the '495 application does

not disclose a structural feature common to all the members of the genus of claim 103 that is correlated to the requirement that the AONs induce skipping of exon 53. In my opinion, the '495 application does not convey possession of the subject matter of claim 103 to a person of ordinary skill in the art.

323. Claim 100 reads:

> 100. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and is capable of inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 3.)

324. I have provided my views on how a person of ordinary skill in the art would interpret claim 100 in paragraphs 215-217 of this declaration.

325. Claim 100 is broader in scope than claim 103 in that it allows for mismatches between the AON and the consecutive 16 to 50 nucleotide complementary part of an exon-internal sequence of exon 53. In my opinion, the '495 application fails to convey possession of the subject matter of claim 100 for the same reason it fails to convey possession of the subject matter of claim 103.

326. In summary, in my opinion, the '495 application fails to describe the full scope of claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103.

C. The Claims in the '210 Application

327. The claims in the '210 application are directed to AONs that induce skipping of exon 51 of the human dystrophin pre-mRNA.

328. The ’210 application discloses only two AONs that are purported to induce skipping of exon 51. AON h51AON1 has the nucleobase sequence ucaaggaagauggcauuucu. (Exh. 2041 at Table 2.) AON h51AON2 has the nucleobase sequence ccucugugauuuuauaacuugau. *Id.* There is no overlap between the sequences of these two AONs. All of the claims in the ’210 application refer to h51AON1. (Exh. 2047 at 1-3.) Consequently, although h51AON2 purportedly induces skipping of exon 51, it should not be a species that is within the scope of the claims of the ’210 application. Consequently, as is the case of the ’495 application, the ’210 application only discloses one species of AON within the scope of the claims.

329. Of course, the lack of predictability for this technology that I have referred to in this declaration, and discussed in the context of written description for the ’495 application claims, applies equally in analyzing whether there is written description support for the claims of the ’210 application (and also the ’992 and ’279 applications).

330. There are four independent claims in the ’210 application, all of which have similar language:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length,
>
> comprising a morpholine ring, wherein said oligonucleotide is capable of binding to an exon internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.
>
> 15. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length,
>
> comprising a peptide nucleic acid and/or locked nucleic acid, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.
>
> 19. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length,

> comprising a 2'-*O*-methyl ribose moiety, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.
>
> 26. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length,
>
> comprising a modification which confers increased resistance to RNAseH, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon internal sequence.

(Exh. 2047 at 1-3.)

331. All of these claims include AONs ranging from 20 to 50 nucleotides in length. And they all require that the AON "is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51." These claims also require that "h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence."

332. This language is similar to the language that appears in claim 78 of the '495 application. Given the broad scope of these claims, in my opinion, the single species disclosed in the '210 application (h51AON1) is not representative of all of the members of the broad genera encompassed by claims 11, 15, 19, and 26.

333. And applying the same analysis set forth above for '495 application claim 78, in my opinion, the '210 application does not provide a description of any structural feature that is common to the members of the claimed genera that correlates with the functional requirement that the AONs induce skipping of exon 51. Given the "capable of binding" language that appears twice in claims 11, 15, 19, and 26, the claims, in my view, embrace tremendously large genera of AONs, all of which must be capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA, and inducing skipping of exon 51. In addition,

h51AON1 must be "capable of binding to said exon-internal sequence." I cannot find any guidance in the '210 application informing a person of ordinary skill in the art of any structural feature that would meet these functional requirements. The only even remotely relevant disclosure is the sequence of h51AON1 itself. But that falls well short of being a feature common to huge sets of AONs encompassed by the claims that allows the AONs to induce skipping of exon 51. As I have mentioned, even minor changes to the nucleotide sequence of an AON can convert a skipping-inducing AON into one that fails to induce skipping. The '210 application does not provide any guidance on the modifications a person of skill in the art could make to the nucleotide sequence of h51AON1 while retaining the ability of this AON to induce skipping.

334. Accordingly, no common structural feature possessed by the species within the genera defined by claims 11, 15, 19, and 26 is disclosed. Without that disclosure, and lacking disclosure of a representative number of species within the genus, the '210 application does not convey possession of the subject matter of claims 11, 15, 19, and 26.

335. Claim 12 reads: "[t]he oligonucleotide of claim 11, 15, 19, or 26, said exon-internal sequence comprising a consecutive part of between 16 and 50 nucleotides of said exon and wherein said oligonucleotide is complementary to said consecutive part." (Exh. 2047 at 1.) This claim tracks the language of claim 79 of the '495 application. Although the genera of claim 12 are more narrow than the genera of claims 11, 15, 19, or 26, the '210 application also fails to convey possession of these groups of AONs. Only a single species (h51AON1) within the genus is disclosed. And while the AONs recited by claim 12 are complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of 51 of the human dystrophin pre-mRNA, the genus still embraces a considerable number of species given (1) the 16 to 50

nucleotide length range permitted and (2) the ability to have mismatched bases in the AON while remaining complementary to exon 51.

336. Although the genera are more narrow, in my opinion, there is no description of a common structural feature possessed by the members of the genera that permits the AONs to induce skipping of exon 51. The unpredictability in the art means that a person of ordinary skill cannot envision which AONs within the genera will induce skipping, and which will not. Consequently, the '210 application does not show possession of the genera of AONs recited by claim 12.

337. Claims 14, 17, 18, 20, 21, and 22 all impose limitations on the chemical backbone contained by the AONs. (Exh. 2047 at 1 and 2.) None of the limitations on the AON chemistry address the bases for the lack of description of claims 11, 15, and 19 that I have mentioned above. In my opinion, the full scope of the subject matter of claims 14, 17, 18, 20, 21, and 22 is not described in the '210 application.

338. Claims 23-25 read as follows:

> 23. The oligonucleotide of claim 11, 15, or 19, wherein the oligonucleotide induces exon 51 skipping of the human dystrophin pre-mRNA and dystrophin expression at the muscle cell upon transfection of primary human muscle cells with at least 100 nM of said oligonucleotide and incubation for at least 16 hours.
>
> 24. The antisense oligonucleotide of claim 23, wherein exon 51 skipping is detected by RT-PCR and/or sequence analysis.
>
> 25. The oligonucleotide of claim 23, wherein dystrophin expression at the muscle cell is detected by immunohistochemical and/or western blot analysis.

(Exh. 2047 at 3.)

339. Claims 23-25 track the language of '495 application claims 88-90. I note that there is no mention in claims 11, 15, or 19 of the "the muscle cell" that is referred to in claim 23. Regardless, claim 23 is directed to conditions which purportedly result in skipping of exon 51.

Claims 24 and 25, although referring to the AON, add requirements relating to how exon skipping is detected, and not requirements on the AON *per se*. None of the requirements of claims 23-25 address the bases for the lack of description which I have identified that exist for claims 11, 15, and 19. In my opinion, the full scope of these claims is not described in the '210 application.

340. Claim 27 reads: "[t]he oligonucleotide of claim 11, 15, 19 or 26 wherein the bases of said nucleotides of said oligonucleotide consist of DNA bases or RNA bases." (Exh. 2047 at 3.) This claim is similar to claim 97 of the '495 application. Limiting the nucleotides of the AONs to DNA bases or RNA bases does not address the deficiencies with respect to the scope of the description that I have identified for claims 11, 15, 19, and 26. In my opinion, the full scope of claim 27 is not described by the '210 application.

341. Claim 28 reads: "[t]he oligonucleotide of claim 11, 15, 19 or 26, said oligonucleotide being less than 50 nucleotides in length." (Exh. 2047 at 3.) This claim is similar to claim 101 of the '495 application. Claim 28 excludes AONs of 50 nucleotides from the claims, leaving within the claimed genera AONs ranging in size from 20 to 49 nucleotides. Claim 28 still covers a very broad collection of claims that is not fully described. In my opinion, the '210 application does not provide a description of the full scope of AONs for claim 28.

342. Claim 29 reads: "[t]he oligonucleotide of claim 11, 15, 19 or 26, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence." (Exh. 2047 at 3.) This is similar to claim 103 in the '495 patent. Although claim 29 narrows the scope of the genera relative to claims 11, 15, 19, or 26, the genera are still very large, and the '210 application only discloses one species that falls within them. And as I have explained, the unpredictability of this technology means that there is no way to know, *a priori*, whether or not

any AONs extending up to 50 nucleotides in length, even if they are capable of binding without mismatches to an exon-internal sequence, will retain the capacity to induce skipping. Consequently, the ’210 application does not disclose a structural feature common to all the members of the genera of claim 29 that is correlated to the requirement that the AONs induce skipping of exon 51. In my opinion, the ’210 application does not convey possession of the subject matter of claim 29 to a person of ordinary skill in the art.

343. In summary, in my opinion, the ’210 application fails to describe the full scope of claims 11, 12, 14, 15, and 17-29.

D. The Claims in the ’992 Application

344. The claims in the ’992 application are directed to methods of using the AONs that are claimed in the ’210 application. Claims 1, 3-7, and 10-27 are for methods for inducing skipping of exon 51 of the human dystrophin pre-mRNA. (Exh. 2050 at 1-3.) Claim 2 for “[a] method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a patient by inducing the skipping of exon 51 of the human dystrophin pre-mRNA.” All of the claims require providing an AON to a cell. (Exh. 2050 at 1.) But the defects with respect to the description of the AONs which I have identified in the ’210 application also apply to the ’992 application. Therefore, for at least the same reasons that the ’210 application does not convey possession of the genera of AONs claimed in that application, the ’992 application similarly does not convey possession of AONs that are used in the methods claimed in the ’992 application.

345. Claim 1 reads:

> 1. A method for inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing **an oligonucleotide of 20 to 50 nucleotides in length** to a cell, **wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1**

> **(UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.**

(Exh. 2050 at 1; emphasis added.)

346. Claim 2 reads:

> 2. A method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a patient by inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing **an oligonucleotide of 20 to 50 nucleotides in length** to a cell of said patient, **wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.**

(Exh. 2050 at 1; emphasis added.)

347. The descriptions of the AONs in claims 1 and 2 are identical. And except for the fact that the AONs in claims 1 and 2 are not limited to any particular chemistry, the claims use the same language as is found in '210 application claims 11, 15, 19, and 26. For example, here is claim 11:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a morpholine ring, **wherein said oligonucleotide is capable of binding to an exon internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.**

(Exh. 2047 at 1; emphasis added.)

348. Given this overlap between '992 application claims 1 and 2 and '210 application claim 11 in terms of how the AONs are defined, in my opinion, the '992 application would not convey to a person of ordinary skill in the art that the AZL applicants had possession of the genus of AONs recited in claims 1 and 2, and therefore the '992 application does not provide written description support for the full scope of the claims.

349. Claims 3-7 and 10-27 all depend, directly or indirectly, from claim 1. Claims 3 and 4 further limit the cells to which the AONs are provided. In claim 3, "the cell is a muscle cell." (Exh. 2050 at 1.) In claim 4, "the cell is from a subject with Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD)." (Exh. 2050 at 1.) Neither of these claims narrows the scope of the AONs that are recited in claim 1. Therefore, the '992 application does not describe the full scope of claims 3 and 4.

350. Claim 5 reads: "[t]he method of claim 1, wherein mRNA produced from skipping of exon 51 of the dystrophin pre-mRNA encodes a functional dystrophin protein or a dystrophin protein of a Becker Muscular Dystrophy patient." (Exh. 2050 at 1.) Like claims 3 and 4, this claim does not narrow the scope of the language that defines the AONs used in the method. Therefore, the '992 application does not describe the full scope of claim 5.

351. Claim 6 reads" "[t]he method of claim 1, wherein the oligonucleotide comprises DNA." (Exh. 2050 at 1.) Claim 7 is essentially the same, except it requires that the "oligonucleotide comprises RNA." *Id.* Claim 24 reads: "[t]he method of claim 1, wherein the bases of said oligonucleotide consist of DNA bases or RNA bases." (Exh. 2050 at 3.) These claims are similar to claim 27 of the '210 application. Limiting the nucleotides of the AONs to DNA bases and/or RNA bases does not address the deficiencies with respect to the scope of the description that I have identified for claim 1. In my opinion, the full scope of claims 6, 7, and 24 is not described by the '992 application.

352. Claim 10-18 require that the AON is modified, either generically (claim 10), or with specified chemistries (claims 11-18). There are similar requirements on the AONs imposed by claims in the '210 application, for example, claims 14, 17, 18, and 20-22, which in my opinion do not render the claims fully described. Reciting such modifications in claims 10-18

does not lead to a different outcome. The '992 application does not provide a written description of the full scope of claims 10-18.

353. Claims 19-21 track the language of '210 application claims 23-25. (Exh. 2050 at 3; Exh. 2047 at 2.) None of the requirements of claims 19-21 address the bases for the lack of description which I have identified that exist for claim 1. In my opinion, the full scope of these claims is not described in the '992 application.

354. Claim 22 reads: "[t]he method of claim 1, said exon internal sequence comprising a consecutive part of between 16 and 50 nucleotides of said exon and wherein said oligonucleotide is complementary to said consecutive part." (Exh. 2050 at 3.) The language in this claim tracks the language in '210 application claim 12. Although the genus of claim 22 is narrower than the genus of claim 1, the '992 application also fails to convey possession of this group of AONs. Only a single species (h51AON1) within the genus is disclosed. And while the AONs recited by claim 22 are complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of 51 of the human dystrophin pre-mRNA, the genus still embraces a considerable number of species given (1) the 16 to 50 nucleotide length range permitted and (2) the ability to have mismatched bases in the AON while remaining complementary to exon 51.

355. Although the genus is more narrow, in my opinion, there is no description of a common structural feature possessed by the members of the genus that permits the AONs to induce skipping of exon 51. The unpredictability in the art means that a person of ordinary skill cannot envision which AONs within the genera will induce skipping, and which will not. Consequently, the '992 application does not show possession of the genus of AONs recited by claim 22.

356. Claim 23 reads: "[t]he method of claim 1, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence." (Exh. 2050 at 3.) The language in this claim tracks the language in '210 application claim 29. Although claim 23 narrows the scope of the genus relative to claim 1, the genus is still very large, and the '992 application only discloses one species that falls within it. And as I have explained, the unpredictability of this technology means that there is no way to know, *a priori*, whether or not any AONs extending up to 50 nucleotides in length, even if they are capable of binding without mismatches to an exon-internal sequence, will retain the capacity to induce skipping. Consequently, the '992 application does not disclose a structural feature common to all the members of the genus of AONs recited by claim 23 that is correlated to the requirement that the AONs induce skipping of exon 51. In my opinion, the '992 application does not convey possession of the subject matter of claim 23 to a person of ordinary skill in the art.

357. Claim 26 reads: "[t]he method of claim 1, said oligonucleotide comprising a modification which confers increased resistance to an endonuclease." (Exh. 2050 at 3.) Claim 27 depends from claim 26, and states that "said endonuclease is RNase H." (Exh. 2050 at 3.) In terms of lack of support in the '992 application, these claims are similar to claims 10-18. Adding a requirement that the AONs are modified to have increased resistance to endonucleases, and specifically to RNase H, does not address the deficient disclosure concerning the genus of AONs embraced by claim 1. Therefore, in my opinion, '992 application does not provide a written description of the full scope of claims 26 and 27.

358. In summary, in my opinion, the '992 application fails to describe the full scope of claims 1-7 and 10-27.

E. The Claims in the '279 Application

359. The claims in the '279 application are directed to methods of using AONs to induce skipping of exon 53, such as those claimed in the '495 application. Claims 1, 3-15, and 22-26 are for methods of inducing skipping of exon 53 of the human dystrophin pre-mRNA. (Exh. 2053 at 2-4.) Claims 2 and 16 are for "[a] method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a subject by inducing the skipping of exon 53 of the human dystrophin pre-mRNA." (Exh. 2053 at 2 and 4.) Claims 20 and 21 are directed to "[a]n expression vector encoding a transcript comprising an oligonucleotide" similar to that described in '495 application claim 78, and a "gene delivery vehicle" comprising the expression vector, respectively. (Exh. 2053 at 4.) All of the method claims require providing an AON to a cell. (Exh. 2053 at 2.) But the defects with respect to the description of the AONs which I have identified for the claims of the '495 application, in particular claim 78, also apply to the claims of the '279 application. Therefore, for at least the same reasons that the '495 application does not convey possession of the genus of AONs defined by claim 78 of the '495 application, the '279 application similarly does not convey possession of the AONs that are used in the methods claimed in the '279 application (or expressed from the expression vectors and gene delivery vehicles of claims 20 and 21).

360. Claim 1 of the '279 application reads:

> 1. A method for inducing the skipping of exon 53 of the human dystrophin pre-mRNA in a subject with Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD), or a cell derived from the subject, said method comprising providing **an oligonucleotide of 15 to 50 nucleotides in length** to said subject or said cell, **wherein said oligonucleotide sequence is capable of binding to an exon internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, wherein said oligonucleotide induces skipping of said exon in the subject or the cell** and wherein mRNA produced from skipping exon 53 of the dystrophin pre-mRNA

encodes a functional dystrophin protein or a dystrophin protein of a Becker subject.

(Exh. 2053 at 2; emphasis added.)

361. Claim 2 reads:

2. A method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a subject by inducing the skipping of exon 53 of the human dystrophin pre-mRNA, said method comprising providing **an oligonucleotide of 15 to 50 nucleotides in length, said oligonucleotide sequence is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and, wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon internal sequence of exon 53 pre-mRNA, and wherein said oligonucleotide induces skipping of said exon in the subject.**

(Exh. 2053 at 2; emphasis added.)

362. The descriptions of the AONs in claims 1 and 2 are identical. And except for the fact that the AONs in claims 1 and 2 are not limited to any particular chemical modifications, the claims use essentially the same language as is found in '495 application claim 78:

78. An isolated antisense **oligonucleotide of 18 to 50 nucleotides in length**, **wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA**, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O*–methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1 and 2; emphasis added.)

363. With respect to the genus of AONs defined by claims 1 and 2, because the length range is greater than the range recited in claim 78 (15-50 nucleotides versus 18-50 nucleotides), claims 1 and 2 recite a broader genus than is recited in claim 78. In addition, the AONs is claims 1 and 2 are not required to have a modification as required by claim 78, although I understand the AONs defined by claims 1 and 2 could have such modification.

364. Given the overlap between ’279 application claims 1 and 2, and ’495 application claim 78 in terms of how the AONs are defined, in my opinion, the ’279 application would not convey to a person of ordinary skill in the art that the AZL applicants had possession of the genus of AONs recited in claims 1 and 2, and therefore the ’279 application does not provide written description support for the full scope of the claims.

365. Claim 3 limits the cell mentioned in claim 1 to a muscle cell. (Exh. 2053 at 2.) Claim 2 does not narrow the scope of the AONs that are recited in claim 1. Therefore, the ’279 application does not describe the full scope of claim 3.

366. Claims 4-10 that the AON is modified, either generically (claim 4) or with specified chemistries (claims 5-10). (Exh. 2053 at 2 and 3.) There are similar requirements on the AONs imposed by ’495 application claims 78, 84, and 86, (Exh. 2045 at 1 and 2), which in my opinion render the claims not fully described. Reciting such modifications in claims 4-10 does not lead to a different outcome. The ’270 application does not provide a written description of the full scope of claims 4-10.

367. Claims 11 and 24 depend from claim 1 and are essentially identical, requiring that the AONs consist of DNA or RNA bases. (Exh. 2053 at 3 and 4.) Claim 25 limits the bases to RNA. (Exh. 2053 at 4.) Limiting the nucleotides of the AONs to DNA bases or RNA bases does not address the deficiencies with respect to the scope of the description that I have identified for claim 1. In my opinion, the full scope of claims 11 and 22 is not described by the ’279 application.

368. Claims 12-14 track the language of ’495 application claims 88-90. (Exh. 2053 at 3; Exh. 2045 at 2 and 3.) None of the requirements of claims 12-14 address the bases for the

lack of description which I have identified that exist for claim 1. In my opinion, the full scope of these claims is not described in the '279 application.

369. Claim 15 depends from claim 1 and requires that the AON "is less than 50 nucleotides." (Exh. 2053 at 3.) Claim 16 has the same requirement, but it depends from claim 2. (Exh. 2053 at 4.) While this language does narrow the genera of AONs recited by claims 1 and 2 by excluding all 50-mer AONs, the genera are still tremendously broad, and in my opinion, they are not fully described by the '279 application for the same reasons that '495 application claim 78 is not fully described.

370. Claim 20 is for an expression vector, and claim 21 is for a gene delivery vector comprising the expression vector. (Exh. 2053 at 4.) The expression vector encodes a transcript comprising an AON that is defined using the same language that appears in claims 1 and 2. Because this genus of AONs is not fully described by the '279 application for the reasons I have explained above, claims 20 and 21 are also not fully described by the '279 application.

371. For claim 22, the AON is 18 nucleotides long and comprises the base sequence of SEQ ID NO: 29. (Exh. 2053 at 4.) Although claim 22 is limited to a single nucleotide sequence, it encompasses unmodified AONs and AONs with modifications to the chemical backbone and modifications to the internucleotide linkages. If we conservatively assume that one position in the AON contains a morpholine ring and the remaining 17 positions could contain a 2'-O-Me, a 2'-O-Me-PS, a morpholine ring, a LNA, or a PNA, that means claim 22 encompasses 5^{17} possible chemical combinations, or more than a hundred billion possible compounds.

372. The AZL applications are directed to AONs and methods of using them for human clinical indications. (Exh. 2041 at [0002].) Consequently, at a minimum, the claimed AONs must be capable of inducing exon skipping within human cells, (Exh. 2041 at [0026]),

which is indeed an express requirement of the method claims in the ’279 application. Given the variability in the chemistry permitted by claim 22, not all of the members of the genus will be capable of inducing skipping within a cell. For example, claim 22 includes a large number of AONs that are minimally modified (or even unmodified), such as those that contain a morpholine ring, or a phosphorodiamidate linkage. Such AONs would be subject to degradation within the intracellular environment.

373. For this reason, the ’279 application does not disclose a common structural feature of the genus of AONs within claim 22 that will permit the AONs to achieve their required function. And only one species within this genus (h53AON1) is described. Given this scant disclosure, the ’279 application does not convey possession of the genus of AONs encompassed by claim 22.

374. Claim 23 depends from claim 1 and states that “said exon-internal sequence” comprises a consecutive part of between 16 and 50 nucleotides of said exon and said oligonucleotide is complementary to said consecutive part.” (Exh. 2053 at 4.) The language in this claim tracks the language of ’495 application claim 79. (Exh. 2045 at 2.) Although the genus of claim 23 is narrower than the genus of claim 1, the ’279 application also fails to convey possession of this group of AONs. Only a single species (h53AON1) within the genus is disclosed. And while the AONs recited by claim 23 are complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of 53 of the human dystrophin pre-mRNA, the genus still embraces a considerable number of species given (1) the 16 to 50 nucleotide length range permitted and (2) the ability to have mismatched bases in the AON while remaining complementary to exon 53.

375. Although the genus is more narrow, in my opinion, there is no description of a common structural feature possessed by the members of the genus that permits the AONs to induce skipping of exon 53. The unpredictability in the art means that a person of ordinary skill cannot envision which AONs within the genera will induce skipping, and which will not. Consequently, the '279 application does not show possession of the genus of AONs recited by claim 23.

376. Claim 26 reads: "[t]he method of claim 1, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence." (Exh. 2053 at 4.) The language in this claim tracks the language in '495 application claim 103. (Exh. 2045 at 4.) Although claim 26 narrows the scope of the genus relative to claim 1, the genus is still very large, and the '279 application only discloses one species that falls within it. And as I have explained, the unpredictability of this technology means that there is no way to know, *a priori*, whether or not any AONs extending up to 50 nucleotides in length, even if they are capable of binding without mismatches to an exon-internal sequence, will retain the capacity to induce skipping. Consequently, the '279 application does not disclose a structural feature common to all the members of the genus of AONs recited by claim 26 that is correlated to the requirement that the AONs induce skipping of exon 53. In my opinion, the '279 application does not convey possession of the subject matter of claim 26 to a person of ordinary skill in the art.

377. In summary, in my opinion, the '279 application fails to describe the full scope of claims 1-16 and 20-26.

VIII. ENABLEMENT

A. Legal Standard

378. I understand that a patent application must enable a skilled artisan to make and use the full scope of the claimed invention without undue experimentation as of the effective filing date of the patent application. This principle is called the "enablement" requirement.

379. I understand that there are a number of factors to consider when making a determination of whether experimentation is undue. These factors include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art and the level of predictability in the art, (4) the level of one of ordinary skill, (5) the amount of direction provided by the inventor and the presence or absence of working examples, and (6) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

380. I understand that when the field of technology is unpredictable and in a very early stage of development, the specification must provide a skilled artisan with a specific and useful teaching. I further understand that in newly developing or "nascent" technologies, it is the specification, not the knowledge of the skilled artisan, that must supply the novel aspects of an invention in order to constitute adequate enablement.

381. As with my analysis of written description, I have been asked to assume that March 21, 2003, the filing date of AZL PCT International Patent Application No. PCT/NL2003/000214 (Exh. 2042), is the relevant date for judging whether the AZL applications comply with the enablement requirement. However, I would reach the same conclusions if I analyzed enablement as of the respective filing dates of the later AZL United States applications.

B. AZL's Claims Are Not Enabled

382. The disclosure of the AZL applications would not enable a person of skill in the art to make and use the claimed inventions without undue experimentation. The various claims

of the AZL applications cover a tremendously large number of AONs with significant structural variability, but the applications disclose just two AONs capable of inducing limited *in vitro* exon skipping for exon 51 and a single AON for exon 53. Exon skipping is extremely unpredictable. Changes to the nucleobase numbers and sequence, chemical backbone, and internucleotide linkages of the AON all influence the ability of the AON to induce exon skipping. Further, the AZL applications provide no clinical data for a nascent technology, which as the AZL applications state, "relates to the restructuring of mRNA produced from pre-mRNA, and therapeutic uses thereof." (Exh. 2041 at [0002].)

383. The disconnect between the expansive scope of AZL's claims and the paucity of its disclosure is borne out in AZL's clinical trials. While the AZL applications state that the AONs disclosed are useful for treating patients with DMD (Exh. 2041 at [0023]), the first and to date only AON that the AZL inventors tested in a Phase III clinical trial *failed* to meet its primary endpoint of a statistically significant improvement in the 6MWT. (Exh. 2039.) That AON, drisapersen, is the same AON disclosed in the AZL applications as h51AON1. (Compare Exh. 2041 at Table 2 with Exh. 2036 at 1515.)

384. I have been asked to discuss in more detail below my consideration of the individual factors that I understand are relevant to enablement as they apply to AZL's claims.

1. The breadth of the claims

385. The breadth of the claims is addressed in the claim interpretation and written description sections above, but is briefly reviewed again here.

386. AZL's interfering claims from the '210 application include claims 11, 12, 14, 15, and 17-29. (Exh. 2047.) All of these claims are directed to AONs capable of binding to exon 51 of the human dystrophin pre-mRNA and inducing skipping of that exon.

387. AZL's interfering claims from the '992 application include claims 1-7 and 10-27. (Exh. 2050.) All of these claims are directed to methods of using AONs capable of binding to exon 51 of the human dystrophin pre-mRNA and inducing skipping of that exon.

388. AZL's interfering claims from the '495 application include claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, 100-103. (Exh. 2045.) These claims are directed to AONs capable of binding to exon 53 of the human dystrophin pre-mRNA (claims 78-79, 84, 86, 88-90, 97-98, 101-103) and/or comprising certain sequences from exon 53 of the human dystrophin pre-mRNA (claims 15 and 76-77, 80, 82, 84, 86, 88-90, 98, 101 and 102) and inducing skipping of that exon.

389. AZL's claims in the '279 application include claims 1-16 and 20-26. (Exh. 2053.) With two exceptions, all of these claims are directed to methods of using AONs capable of binding to exon 53 of the human dystrophin pre-mRNA and inducing skipping of that exon. The two exceptions are claims 20 and 21. Claim 20 is for an expression vector encoding a transcript comprising an AON capable of binding to exon 53 and inducing skipping of that exon. Claim 21 is for a gene delivery vehicle comprising the expression vector.

390. Thus, all of the exon 51 and many of the exon 53 claims are "functional" claims—the claims do not offer any meaningful structure, formula, chemical name, or physical properties that would limit the breadth of the AONs encompassed by the claims. Instead, they are directed to the "functional" properties of being "capable of binding" to a target region of exons 51 or 53 and "inducing the skipping" of that exon. Even with a conservative analysis, these claims encompass a tremendously large number of compounds.

391. The remaining "comprising" claims relating to exon 53 are also exceedingly broad. For example, claim 15 requires that the AON be 15 to 80 nucleotides in length; contain 15 nucleobases from the 18-mer "cuguugccuccgguucug"; and contain a single modification

selected from a variety of possible backbone and internucleotide linkage modifications. See paragraphs 191-197. But this encompasses a tremendous amount of chemical variation. For example, adding a single nucleobase to a 15-mer yields 8 possible sequence combinations (A, C, G, or U added before or after the 15-mer.) Adding two nucleobases yields 64 possible combinations. Adding three nucleobases yields 256 combinations. Adding 35 nucleobases to obtain a 50-mer yields 42,501,298,345,826,806,923,264 possible combinations. See paragraph 192.

392. Of course, this substantially ***underestimates*** the size of the claimed genus because it does not account for modifications to the chemical backbone, modifications to the internucleotide linkages, and the use of natural and non-natural modified bases. Like the "capable of binding" claims, claim 15 encompasses an immense number of possible AONs.

393. The dependent claims do not meaningfully limit claim scope. While they might place some restriction on either the nucleobase sequence, the chemical backbone, or the internucleotide linkages, they never do so in combination, such that even the relatively smaller claimed genera still encompasses a tremendous number of possible AONs.

2. The nature of the invention

394. AONs are complex chemical compounds that can theoretically form Watson-Crick interactions with target pre-mRNA sequences and induce exon skipping. However, exon skipping is very unpredictable and many complications have prevented successful clinical use of AONs.

395. The AZL applications disclose the nucleobase sequence of two 2'-O-Me-PS AONs designed to induce exon skipping from exon 51 and two 2'-O-Me-PS AONs designed to induce exon skipping from exon 53. The AZL applications disclose use of standard *in vitro* transfection techniques to assay skipping, with no clinical or *in vivo* data reported. Even in

controlled *in vitro* experiments, only one of the exon 53 AONs was reported as successfully inducing exon skipping.

3. The state of the prior art / Level of predictability in the art

396. A skilled artisan would have viewed exon skipping AONs as a nascent technology in 2003.

397. No exon skipping drugs had ever been commercially marketed. This remains true today.

398. There were limited options for delivering AONs *in vivo*, and an absence of suitable animal models for studying the effect of exon skipping on human dystrophin. It was also unclear whether adequate dystrophin protein could ever be produced to treat DMD.

399. Even *in vitro*, I am not aware of any AON longer than 40 nucleotides in length that had been tested for exon skipping of any gene.

400. It was, and is, difficult to predict which AONs are capable of inducing exon skipping, even *in vitro*. (Exh. 2012 at 1548; Exh. 2010 at S76.)

401. A 2007 paper co-authored by several members of the AZL group states that "several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], ***there are still no clear rules to guide investigators in their design***, and in mouse and human muscle cells *in vitro* there is great variability for different targets and exons." (Exh. 2013 at 807; emphasis added.)

402. While software such as RNA mfold could be used to predict the two-dimensional structure of RNA, that software could not accurately predict the three-dimensional structure of RNA and was therefore of marginal use in designing exon skipping AONs. This software, which I believe was developed in the late 1980's, predicts minimum free energy for folds containing any particular base pair. And because the software ignores 3-D interactions of the mRNA, as

well as protein-RNA interactions, its secondary structure predictions do not always correspond to the true biological fold of the pre-mRNA, that is, the functional RNA fold as it exists in cells. As the AZL group wrote in 2009, "in general ***a trial and error procedure*** is still involved to identify potent AONs." (Exh. 2014 at 548; emphasis added.)

403. As I mentioned above, small changes in sequence and structure have significant and unpredictable impacts on the ability of an AON to induce exon skipping in the dystrophin pre-mRNA. If an AON does not bind with sufficient affinity, it will not adequately induce exon skipping. If an AON binds too tightly, it also will not induce adequate exon skipping. In the absence of empirical testing, one cannot know whether or not a particular AON would induce skipping, even *in vitro*.

404. Modifications to the nucleobases, chemical backbone, and internucleotide linkages all affect skipping, as does selection of the target tissue. (Exh. 2013 at 807; Exh. 2005 at 173.) Moreover, mismatches unpredictably alter efficacy of AON exon skipping activity, as does the creation of "hybrid" AONs having multiple chemical modifications. Because different AON chemistries influence binding affinity, each type of AON will have different binding characteristics, even with identical nucleobase sequences. This prevents meaningful extrapolation from one AON to another.

405. In 2003, there were no suitable means of administering AONs for treating DMD. As the AZL investigators explained in a scientific publication paralleling the disclosure of the AZL applications, "***provided that a suitable means of administration for the AONs is developed***, antisense-induced reading frame correction ***will be*** a promising therapeutic approach for many DMD patients carrying different deletions and point mutations." (Exh. 2018 at 911; *see also* Exh. 2025 at 450 (emphasis added); "***significant development will be necessary to***

improve the delivery aspects of AON before the antisense approach could be regarded as a realistic therapeutic option in DMD.")

406. While the Sarepta clinical trials with eteplirsen (a 30-mer PMO) offer a ray of hope, the unpredictability and challenge of successfully delivering exon skipping AONs to treat patients certainly remains true today.

407. In sum, as of 2003 (and even today), the generation of an AON that induced skipping of exons 51 or 53 of the *DMD* gene was far from routine for a skilled person and would not have been predictable. Because of this lack of predictability, the skilled person would have been required to make and test each AON to determine whether it was capable of inducing exon skipping. The generation of AONs that provide a therapeutic effect, e.g., as evidenced by the 6 minute walk test, would have been even more unpredictable.

408. Indeed, even today, there are no approved exon skipping therapies. In 2013, the AZL group's exon 51 candidate, which is the AON h51AON1 disclosed in the AZL applications, failed to meet its primary endpoint in Phase III clinical trials.

4. The level of one of ordinary skill

409. The person of ordinary skill in the art is described above in paragraph 179. For the reasons described above, this person would have had to empirically test each individual AON to determine whether or not it induced exon skipping *in vitro*. In the absence of undue experimentation, this person would not have been able to make and use the full scope of AONs included within the scope of the claims. Because of the unpredictability of the science, this person would not have known how to make AONs that could actually be used to treat patients with DMD.

5. The amount of direction provided by the inventor and the presence or absence of working examples

410. As described above, the AZL applications report that two AONs, h51AON1 and h51AON2, are capable of inducing skipping of exon 51 *in vitro*. The AZL applications disclose only a single AON, h53AON1, capable of inducing skipping of exon 53 *in vitro*.

411. All three of these AONs (and all of the AONs described in the AZL applications) are 2'-O-Me-PS AONs. (Exh. 2041 at [0047].)

412. All three of these AONs (and all of the AONs described in the AZL applications) contained exclusively the natural nucleobases found in RNA, A, C, G, and U. (Exh. 2041 at Table 2.)

413. h51AON1 is 20 nucleotides in length; h51AON2 is 23 nucleotides in length; and h53AON1 is 18 nucleotides in length. The AZL applications report that neither AON length nor percent G/C content correlated to their effectivity in exon skipping. (Exh. 2041 at Table 2.) Moreover, no AON longer than 24 nucleotides is tested in the AZL applications. (Exh. 2041 at Table 2.)

414. No morpholino, LNA, PNA, or hybrid AONs were tested or described.

415. Because there are no AONs incorporating these modifications disclosed in the AZL applications, regardless of how the claims are interpreted, there is not a single example of an AON within the scope of claims 11, 14, 15, 17, 18 of the '210 application, claims 2, 6, 7, and 18 of the '992 application, claims 84, 86, and 98 of the '495 application, and claims 6, 8-10 of the '279 application, which all require a chemical modification other than 2'-O-Me-PS.

416. For the remaining claims, despite the immense number of AONs potentially within the scope of each claim, the specification discloses one or at most two "non-representative" examples. These examples are "non-representative" of the species within the

scope of the claims because they are 2'-O-Me-PS AONs of very limited length (relative to the lengths permitted by the claims) containing no mismatches, no non-natural bases, and no additional or alternative chemical modifications.

417. The AZL applications do not disclose any AONs comprising a single modification such as a morpholine ring, a PNA, a 2'-O-methyl ribose moiety, a phosphorothioate internucleoside linkage, or "a" phosphorodiamidate internucleoside linkage, rather than AONs having all 2'-O-Me-PS modifications. The AZL applications also do not disclose any AONs, such as mixmers or gapmers, that have more than one type of modification.

418. The longest AON disclosed in the AZL applications is only 24 nucleotides, while the claims recite AONs of up to 50 or 80 nucleotides in length. In my opinion, AONs approaching these lengths will not efficiently induce exon skipping, if they induce it at all, for a number of reasons, such as access to the complementary sequence in the pre-mRNA, binding affinity of the AON for the complementary sequence, and the ability to transfect longer AONs into cells.

419. The applications purport to provide guidance in selecting target sequences by recommending exon targets having partially "open" and partially "closed" structures. (Exh. 2041 at [0006]-[0009].) But this is not particularly meaningful. First, consistent with my own experience and as acknowledged repeatedly in the scientific literature, a skilled person needs to do the empirical test to determine whether or not a given AON can induce skipping. Second, the "guidance" hasn't borne out in the scientific literature, as I have explained above in my discussion of the publications by the AZL group. Third, nothing in the claims reflects this guidance, as the claims are not limited to AONs targeting both "open" and "closed" structures in the dystrophin pre-mRNA.

420. The AZL applications disclose that the claimed AONs can be used to treat patients with DMD, but no clinical data is provided demonstrating therapeutic efficacy. The AZL applications do not provide any dosing recommendations, any information about methods of administration, or any formulations suitable for administration to patients. The AZL applications do not even include any animal studies or other *in vivo* experiments.

6. The quantity of experimentation needed to make or use the invention based on the content of the disclosure

421. The AZL applications exemplify an invitation to experiment. The named inventors identified two exon 51 sequences and one exon 53 sequence capable of inducing *in vitro* exon skipping. These AONs were synthesized as 2'-O-Me-PS.

422. Yet each of the claims at issue conservatively encompasses a tremendously large number of possible chemical compounds, and exon skipping is an unpredictable field. In order to determine whether or not a given AON is capable of inducing exon skipping, even *in vitro*, one must therefore experiment on each different AON.

423. Even making a small number of these compounds represents a massive investment of time and effort. For example, synthesizing a 30-base morpholino AON takes approximately two weeks. Hybrid AONs containing morpholinos and non-natural bases could take longer. *In vitro* transfection and the subsequent RT-PCR study conservatively takes several days. Thus, testing a single morpholino AON would take on the order of 2.5-3 weeks. Even making and testing a single 2'-O-Me-PS AON, which is easier to synthesize, would take on the order of 3-5 days. And this is just to determine *in vitro* efficacy using a screening procedure that does not examine production of dystrophin protein.

424. This is where the claim scope is highly problematic. The claims cover a tremendously large number of compounds. Because of the unpredictability of exon skipping,

practicing the full scope of the claimed invention would require synthesizing and testing each of these compounds. This undisputedly requires a tremendous amount of experimentation.

425. In essence, the AZL applications disclose a starting point for further iterative research in an unpredictable field. Even synthesizing candidate compounds would, in and of itself, require a tremendous quantity of experimentation, and in the case of hybrids with modified bases, require unconventional and possibly untested synthetic schemes. Putting those synthesis challenges aside, testing the compounds would then collectively take an immense amount of time and effort. Yet the AZL applications offers very limited guidance in terms of representative species and no guidance in terms of common structures.

426. The quantity of experimentation needed to use the invention to treat patients is staggering. In addition to selecting a suitable nucleobase sequence, suitable backbone chemistry, and suitable internucleotide linkage, the skilled person would need to develop a dosage and administration regimen as well as a suitable formulation. With no guidance from the applications, the skilled person would also need to overcome the delivery challenges that have largely prevented the development of therapeutic AONs. In the words of a paper co-authored by Dr. van Ommen of the AZL group, "***significant development will be necessary to improve the delivery aspects of AON before the antisense approach could be regarded as a realistic therapeutic option in DMD***." (Exh. 2025 at 450; emphasis added.)

427. As I stated in a 2013 review, this is "no small task." (Exh. 2005 at 179.)

C. The AZL Applications Do Not Disclose Any AONs that Demonstrate Sufficient Exon Skipping to Provide a Therapeutic Effect

428. The stated use for the claimed AONs is the treatment of DMD. As stated in the AZL applications "Any oligonucleotide fulfilling the requirements of the invention may be used to induce exon skipping in the DMD gene." (Exh. 2041 at [0016].) This "results in proteins

similar to those found in various BMD patents. A survey of the Leiden DMD mutation database learns that we can thus correct over 75% of DMD causing mutations (see Table 4)." (Exh. 2041 at [0017]; citations omitted.)

429. But there is no evidence in the AZL applications or elsewhere that the sequences disclosed in these applications demonstrate sufficient exon skipping to provide a therapeutic effect.

430. Indeed, as discussed above, when the AZL group selected an exon 51 candidate to take into the clinic, they chose drisapersen, a 2'-O-Me PS AON having the following nucleobase sequence: UCAAGGAAGAUGGCAUUUCU. (Exh. 2036 at 1515; Exh. 2037 at 987.) This is the same exon 51 candidate identified in the AZL applications as h51AON1. (*Compare* Exh. 2041, Table 2.)

431. Although Prosensa continues to investigate the possibility of some benefit from drisapersen in treating young, relatively healthy DMD patients, this therapeutic failed in a phase III clinical trial: drisapersen did not meet the primary endpoint of a statistically significant improvement in the 6MWT compared to placebo. (Exh. 2039.) There was also no treatment difference in key secondary assessments of motor function, including the 10-meter walk/run test, 4-stair climb, and North Star Ambulatory Assessment.

432. In sum, while the AZL applications suggest a therapeutic use of treating DMD by skipping exon 51 or 53 in patients, not a single AON sequence has been disclosed that provides such an effect.

433. For these reasons, in my opinion, all of the claims in the '495, '210, '992, and '279 applications are not enabled.

IX. INDEFINITENESS

A. Legal Standard

434. I understand that claims in a patent application must be definite. I have been informed that a claim is considered indefinite if the claim, when read in the context of the patent application and the record of the examination of the patent application by the Patent Office, fails to inform, with reasonable certainty, those skilled in the art about the scope of the invention. I understand that this definiteness requirement is evaluated in the context of the filing date of the patent application. I have applied my understanding as set forth in this paragraph in evaluating the claims in the AZL applications.

435. As mentioned, I have reviewed the AZL applications. I have also been provided with, and have reviewed, excerpts from the prosecution of the '495 (Exh. 2054), '210 (Exh. 2055), '992 (Exh. 2056), and '279 (Exh. 2057) applications.

436. Based on my review of these materials, in my opinion, the claims in the AZL applications do not inform a person of ordinary skill in the art of their scope with reasonable certainty, and are therefore indefinite. I set forth my reasoning below.

B. The "Capable of Binding" Claims

437. Claim 11 of the '210 application is representative of the claims that include the "capable of binding" language:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a morpholine ring, **wherein said oligonucleotide is capable of binding to an exon internal sequence of exon 51 of the human dystrophin pre-mRNA** and inducing skipping of exon 51 **wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence**.

(Exh. 2047 at 1; emphasis added.)

438. Claim 11 refers to two separate molecules as being "capable of binding" to a particular sequence. First, the AONs recited by the claim must be capable of binding to an unspecified exon-internal sequence of exon 51 of the human dystrophin pre-mRNA. Second, a particular AON, h51AON1, must also be capable of binding to that exon-internal sequence.

439. All of the claims in the '210 application include this first and second "capable of binding" language. (Exh. 2047 at 1-3.)

440. All of the claims in the '992 application include this first and second "capable of binding" language. (Exh. 2050 at 1-3.) The same is true for all of the claims of the '279 application (although with respect to exon 53). (Exh. 2053 at 2-4.)

441. Many of the claims of the '495 application, including claims 78, 79, 82, 84, 86, 88-90, 97, 98, and 100-103, include analogous language, but they differ in that the AONs claimed in this application are directed to inducing skipping of exon 53 instead of exon 51. (Exh. 2045 at 1-4.) For example, claim 78 reads:

> 78. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is **capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA** and inducing skipping of exon 53, and wherein **h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA**, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O*–methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1 and 2; emphasis added.)

442. And claim 100 reads:

> 100. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein **said oligonucleotide is complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA** and is capable of inducing skipping of exon 53, and wherein **h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA**, said

> oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 3; emphasis added.)

443. As discussed in paragraph 210, there is no definition of "exon-internal sequence" provided by the AZL applications. But the AZL applications do inform the reader that "[t]he skipping of an exon can be induced by the binding of antisense oligoribonucleotides (AONs) targeting either one or both of the splice sites, or exon-internal sequences." (Exh. 2041 at [0015].) Given this disclosure, it is unclear what the AZL applicants intended. Does the "exon-internal sequence" of exon 53 mean the entire exon, or the entire exon excluding the terminal nucleotides as they are locations that are involved in splice site recognition?

444. Moreover, the AZL applications do not differentiate the sequences of an "exon-internal sequence" that when bound by an AON will induce skipping, from those that when bound do not. A person of ordinary skill in the art is left to fend for herself in terms of defining what is meant by "exon-internal sequence" as that term is intended to be understood in the context of the "capable of binding" claims. In addition, there are no conditions expressed in the claims, or disclosed in the AZL applications, under which the required binding will occur.

445. The prosecution excerpts I have reviewed do not provide any guidance on the proper interpretation of this claim term.

446. The lack of clarity as to the scope of these claims is compounded by the second "capable of binding" clause. Referring back to claim 11 of the '210 application as an example, the claim states that "h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence." No conditions for binding are specified in the claim, the application, or the file history, so it is unclear how a skilled person should

determine whether the claimed AON and h51AON1 should be tested to determine whether or not they are "capable of binding" the exon-internal sequence. There is no disclosure in the AZL applications concerning how "binding" of the AON to the "exon-internal sequence" of the pre-mRNA is assayed or measured. The AZL applications do not disclose to a person of ordinary skill in the art how to reach a conclusion that the AON has bound, other than by reference to the separate and distinct functional requirement recited in claim that exon skipping is induced.

447. Hybridization (binding) of nucleic acids is exquisitely sensitive to conditions such as, for example, temperature, salt concentration, and complementarity of the AON with the exon-internal sequence. Under any set of hybridization conditions, h51AON1 and the claimed AON may both bind to "said" sequence in exon 51, or they may not. There simply is no way to know when the conditions are not specified. They are not specified in any of the "capable of binding" claims. And they are not specified in the AZL applications.

448. Additionally, it is unclear if the person of ordinary skill in the art should use the same conditions for binding of the claimed AON and h51AON1. The claims do not require it, and the specification and prosecution excerpts provide no guidance.

449. Referring still to claim 11 as an example, a significant additional layer of ambiguity exists in that both the claimed AON and h51AON1 are capable of binding to "said exon-internal sequence." It is unclear whether this means that h51AON1 must bind to the exact same exon-internal sequence as is bound by the claimed AON, a subset of the sequence, or simply to the same exon. Nor does the claim provide any guidance as to the conditions under which the claimed AON and h51AON1 bind to the "said exon-internal sequence." "Binding" is never measured in the AZL applications. It is merely inferred from the downstream readout of exon skipping.

450. For example, suppose h51AON1 and the claimed AON bind to overlapping, but non-identical sequences. Are both AONs binding to the same "exon-internal sequence?" How much overlap is necessary to fall within the scope of the claim? h51AON1 is 20 nucleotides long. Suppose it overlaps with the binding site of the claimed AON for 10 of the 20 bases; or 5 bases; or 1 base. Do each of these scenarios fall within the scope of the "capable of binding" claims? Or only some of them? Or none? A skilled person could not, with reasonable certainty, determine whether these overlapping AONs are within the scope of claim 11.

451. Even if "said exon-internal sequence" is determined to exclude this type of non-identical overlap, and even disregarding the lack of specified hybridization conditions, there is still ambiguity in these claims. For example, assume the claimed AON is 50 nucleotides in length and it binds to 50 complementary nucleotides within the exon-internal sequence of exon 51 (and induces skipping). For this example, we can arbitrarily identify those nucleotides within the exon-internal sequence as nucleotides 101-150. Assume that h51AON1 binds to the nucleotides at 111-130. In this instance, h51AON1 binds to a portion (actually 2/5) of "said exon-internal sequence." It is not clear from the claims, the AZL applications, or the prosecution excerpts I reviewed whether under these facts the 50-mer AON in my example falls within the scope of claim 11.

452. None of the dependent "capable of binding" claims address these ambiguities in the scope of the claims.

453. For each of these reasons, a person of ordinary skill in the art would not be informed, with reasonable certainty, about the scope of any of the "capable of binding" claims in the '495, '210, '992, and '279 applications.

C. The "Comprising" Claims

454. The "comprising" claims includes claims 15, 76, 80, 82, 84, 86, 88-90, 98, 101, and 102 of the '495 application.[7] (Exh. 2045 at 1-3.) Independent claim 15 is representative of these claims:

> 15. An isolated antisense oligonucleotide of 15 to 80 nucleotides comprising at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29) wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-O –methyl, 2'-O-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1.)

455. As I have explained in paragraphs 191-197, claim 15 encompasses a tremendous number of molecules having different lengths, nucleobase compositions, and backbone and internucleotide linkage modification. The claims that depend from claim 15 do not meaningfully limit the scope of the claims.

456. Despite the broad scope of the "comprising" claims, the AONs within the scope of the claims must all "induce[ ] exon 53 skipping in the human dystrophin pre-mRNA."

457. Given the unpredictability in this technology, as I have discussed previously in my declaration, there is no way of knowing, *a priori*, if any given AON falling within the broad scope of the structural parameters relating to nucleotide length, nucleotide composition, and or modification that are recited in the claim will also meet the functional requirement that the claim induces skipping. The genus is simply too broad, and the technology too unpredictable, to

[7] Claims 82, 84, 86, 88-90, 98, 101, and 102 are also mentioned in the context of the "capable of binding" claims because they depend from a "capable of binding" claim and from a "comprising" claim.

permit a person of ordinary skill in the art to determine with reasonable certainty which AONs that satisfy the structural requirements of the "comprising" claims will also possess the required functional characteristics.

458. In addition, while the "comprising" claims all require that the AONs induce skipping, there is nothing in the claims clarifying how much skipping the AON must cause. Any skipping, even if undetectable? Any level of detectable skipping? How is the skipping determined experimentally and what AON concentration is used to induce skipping? A level of skipping that will achieve a therapeutic effect, given that "the invention relates to the restructuring of mRNA produced from pre-mRNA, and therapeutic uses thereof"? (Exh. 2041 at [0002].) When exon skipping is measured under one set of conditions an AON meeting the structural features of the claims might be found to meet the structural requirement os inducing skipping, but when measured under another set of conditions it may not. Consistent with this concern, Heemskerk *et al*. state that "[d]ue to different experimental designs with regard to AON length, sequence, dose and injection frequency, it is difficult to draw conclusions on the relative efficiencies of 2OMePS and PMO AONs." (Exh. 2020 at 258.) These authors go on to state that they observed for "the first time … exon skipping and protein production in the heart ... after systemic delivery of unconjugated AONs." (Exh. 2020 at 265.) They go on to state that "[c]ompared to other studies with unconjugated AONs ... we applied a higher dose over a shorter period of time, which might explain why other studies have failed to detect exon skipping and protein production in heart tissue to date." *Id.* They also attribute their different result to the detection method used ("In addition, we assessed protein levels with the Odyssey system, which may be more sensitive than traditional methods."). *Id.* These statements are consistent with my experience that multiple variables will have an impact on whether or not skipping is detected.

459. Moreover, except for certain claims, discussed below, the claims do not inform a person of ordinary skill in the art how to measure exon skipping. Given this lack of specificity, and the known difficulties in comparing skipping across different laboratories, one cannot be certain which AONs are within the scope of the genus and which AONs are not. As of March 2003, and to some extent still even today, there is a lack of standardized procedures in place for quantifying dystrophin production, which is a recognized obstacle to the development and evaluation of exon skipping AONs. (Exh. 2028 at 1 and 2 ("In a pilot study comparing the sensitivity and reliability of the preferred individual laboratories' methodologies, we found significant levels of inter- and intralaboratory variability (data not shown).").) When exon skipping is measured under one set of conditions, an AON meeting the structural requirements of the claim might also be shown to meet the functional requirement. When skipping is measured under another set of conditions, it may not. In other words, under a broad interpretation where any means of measuring exon skipping is permitted, some AONs may fall within the scope of the "comprising" claims, but when exon skipping is measured in another way, they may not.

460. The AZL applications disclose experiments where the ability of AONs to induce skipping is tested in cells from DMD patients (Example 1) and cells from "a non-affected individual" (Example 2). (Exh. 2041 at [0041] and [0048].) The type of cells used in such experiments can have an impact on level of skipping that occurs. As stated in the AZL application, "the levels of exon skipping observed in the DMD patient cells are significantly higher than those previously obtained in human control cells." (Exh. 2041 at [0035].) Given this disparity in expression, an AON that weakly induces skipping might be detected as a skip-inducer in assays utilizing DMD patient cells, but would not be detected in non-patient cells. In other words, the assay culture conditions would have an impact in determining whether an AON

is within, or without, the scope of the claims. This is in addition to the impact of the assay used to detect skipping.

461. Other related factors that could have an impact on skipping include the concentration of AON used in the experiments, the use of transfection agents to facilitate getting the AONs into the cells, the conditions the cells are grown under, and the amount of time post-transfection at which samples are taken for analysis of skipping. None of these parameters are specified by the "comprising" claims, and all of them, based on my experience, may have impact on the level of skipping obtained from any given AON.

462. Claim 88 of the '495 application imposes limitations on the cells wherein skipping (human muscle cells, although there is no requirement for DMD patient or normal cells) is induced, the concentration of AON used in transfection (at least 100 nm), and incubation for at least 16 hours. (Exh. 2045 at 2.) While these aspects do provide some framework to assessing the ability of an AON to induce skipping, still many sources of variability are not defined.

463. One of those sources of variability is the methodology used to detect exon skipping. In the AZL applications, the methods disclosed include RT-PCR (and sequencing of the RT-PCR product), Western blot, and immunohistochemical analysis. (Exh. 2041 at [0042], and [0044]-[0046].) In my experience, these methods have very different sensitivities and so a weakly skip-inducing AON might be detected by methods having more sensitivity, while less sensitive methods would not reveal any skipping. Although RNA detection assays are the most sensitive because they typically involve amplification of the RNA by PCR, detection of protein is crucial as it is the measure which is of the most clinical relevance. However, protein assays are typically much less sensitive than RNA amplification assays and are more fraught with quantification challenges. In addition to sensitivity and method of detection of the RNA or

protein, there is also the issue of stability kinetics and relationship to the time of analysis. The RNA is typically much less stable (implying that at later times this would not be detectable), whereas the protein is more stable.

464. Claims 89 and 90 limit detection of the products of skipping to the disclosed techniques. (Exh. 2045 at 3.) Nonetheless, no particular level of skipping is required by the claims. Nor do the AZL applications provide any indication of the sensitivity of these assays.

465. In my opinion, a person of ordinary skill in the art would not be able to determine whether or not a particular AON falls within the scope of the "comprising" claims in the '495 application.

466. For these reason, the claims in the '495, '210, '992, and '279 applications are indefinite.

X. THE MATERIAL LIMITATIONS OF THE '210 APPLICATION CLAIMS ARE NOT FOUND IN THE CLAIMS OF THE EARLIER-FILED AZL APPLICATIONS

467. I have been informed that United States patent law imposes a one year deadline for filing claims that interfere with the claims of an issued patent. I have also been informed that there is an exception to this one year deadline when a party has been claiming at some earlier time the same or substantially the same invention as that claimed in the issued patent. I have been informed that claims filed after the one year deadline are deemed to meet this exception when they are not materially different from claims that were present in the application, or a predecessor application, before the one year critical date. Finally, I have been informed that there is a presumption that claim limitations added in response to an examiner's rejection are material when those limitations result in allowance of the claims.

468. With the above legal principles in mind, I have been asked to provide my opinion on whether the material limitations of the '210 application claims are found within the earlier

filed claims of United States Patent Application No. 12/976,381 ("the'381 application"), United States Patent Application No. 12/198,007 ("the '007 application"), or the '495 application (collectively "the predecessor applications"). In my analysis, I have reviewed selected portions of the prosecution history of the '210 application, and its predecessor applications. For the reasons discussed below, it is my opinion that the material limitations of the '210 application claims are not found in the predecessor applications.

A. The Material Limitations of the '210 Application

469. As I discussed above in paragraphs 228 and 229, above, the four independent claims in the '210 application are all essentially the same except for the recited chemical modifications. Because the only difference in these claims is the chemical modification, my analysis of the material limitations of these claims will focus on amendments made to claim 11.

470. The following is a brief overview of the prosecution history of claim 11 of the '210 application. In providing this overview, I stress that I am not an expert in patent law or the various interactions that occur between the United States Patent and Trademark Office and a patent applicant. Thus, I have relied on the attorneys representing UWA to assist me in identifying the relevant rejections made by the examiner, and the corresponding amendments made by the applicants. However, the opinions discussed herein remain my own.

471. As extensively discussed above, it is my opinion that the claims of the '210 application lack written descriptive support, are not enabled, and are indefinite. However, solely for the purpose of identifying the material limitations of the '210 application claims and determining whether those limitations are supported by the claims of the predecessor applications, I have been asked to assume that the '210 application claims do have written descriptive support.

472. Claim 11 was first filed in a preliminary amendment[8] dated January 3, 2013. As originally filed, claim 11 recited:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, said oligonucleotide comprising a sequence which is complementary to a target nucleic acid sequence of exon 51 of the human dystrophin pre-mRNA, wherein the target nucleic acid sequence comprises a nucleotide sequence that is complementary to the sequence UCAAGGAAGAUGGCAUUUCU (SEQ ID NO: 27).

(Exh. 2062.) I have been informed that the examiner rejected this claim for a number of reasons, including that it was drawn to non-eligible subject matter because the claims cover naturally occurring nucleic acids.[9]

473. In response to the examiner's rejection, claim 11 was amended on January 21, 2014 to recite: [10]

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, said oligonucleotide comprising a nucleotide sequence which is complementary to a target ~~nucleic acid~~ sequence of exon 51 of the human dystrophin pre-mRNA, wherein ~~the~~ said target ~~nucleic acid~~ sequence comprises a nucleotide sequence that is complementary to the sequence UCAAGGAAGAUGGCAUUUCU (SEQ ID NO: 27) and wherein said oligonucleotide comprises a morpholine ring.

[8] I have been informed that a preliminary amendment is an amendment filed by the applicant before the first office action has been mailed by the examiner.

[9] I understand that the examiner first issued an office action on September 11, 2013 that did not reject the claims as directed to non-eligible subject matter. However, I have been informed that the examiner vacated the original office action, and subsequently issued another office action with the non-eligible subject matter rejection on September 27, 2013.

[10] I have reproduced claim 11 as it appears in the Applicants' response to the examiner's office action. I have been informed that strikethroughs indicate deleted claim elements, and underlining indicates added claim elements.

(Exh. 2063.) In the remarks accompanying the amendment, the applicants stated that claim 11 was amended to refer to an oligonucleotide that comprises a modified nucleotide, and thus recites a non-naturally occurring nucleic acid. Because this limitation was added in response to the examiner's rejection, and was necessary for the claims to ultimately be allowed, the recitation of a modified nucleotide is a material limitation of the '210 application claims.

474. The '210 application claims were next amended on May12, 2014 to their current form. As amended, claim 11 recites:

> 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a morpholine ring, wherein said oligonucleotide ~~comprising a nucleotide sequence which is complementary to a target sequence~~ is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein ~~said target sequence comprises a nucleotide sequence that is complementary to the sequence~~ h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequences ~~and wherein said oligonucleotide comprises a morpholine ring.~~

(Exh. 2064.) In the remarks accompanying those amendments, Applicants identified where the current amendments are allegedly supported in the '210 application specification.

475. I have been informed that based on these amendments, the examiner allowed the '210 application claims. I have reviewed the Notice for Allowance, and note that it states that the claims submitted on January 14, 2014 were not adequately supported by written description. (Exh. 2076.) However, it is the examiner's opinion that the claims submitted on May 12, 2014 have adequate support in the '210 application specification.

476. Because the claim amendments submitted on May 12, 2014 were necessary for the claims to be allowed, they constitute material limitations. Specifically, the material limitations of the '210 application claims are:

(1) the antisense oligonucleotide comprises a modified nucleotide, i.e., morpholine ring (claim 11), peptide nucleic acid and/or locked nucleic acid (claim 15), 2'-*O*-methyl ribose moiety (claim 19), or a modification which confers increased resistance to RNAseH (claim 19);

(2) the antisense oligonucleotide is capable of binding to an exon-internal sequence;

(3) the antisense oligonucleotide is capable of inducing skipping of exon 51 (after binding to the exon-internal sequence); and

(4) h51AON1 (SEQ ID NO: 27) is also capable of binding to the same exon-internal sequence that the claimed antisense oligonucleotide is capable of binding.

477. As discussed in paragraphs 230 and 231, with the exception that the oligonucleotide comprises a modification, the material limitations of the '210 application claims are functional limitations. Accordingly, the claims of the predecessor applications must claim the same functional limitations as found in the '210 application claims. Moreover, given the lack of description in the '210 application as to any structural feature that correlates with the function al requirement that the oligonucleotide induce skipping of exon 51 (see paragraphs 333 and 334), it is my opinion that the predecessor application claims must recite this limitation explicitly.

478. In addition, as discussed in paragraphs 449-451, it is my opinion that the material limitation reciting "h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to the same exon-internal sequence" is ambiguous. Due to this ambiguity, it is my opinion that the predecessor application claims must recite this limitation explicitly. That is, in my opinion it is not enough to simply claim SEQ ID NO: 27.

B. The Predecessor Application Claims Do Not Claim the Functional Material Limitations of the '210 Application Claims

479. The '816 patent issued on October 5, 2010. I have been informed that this means claims that interfere with the '816 patent must have been filed before October 5, 2011. However, the '210 application was not filed until July 16, 2012. For this reason, I have been

informed that the material limitations of the'210 application claims must find support in the earlier filed claims of its predecessor applications. Accordingly, I have reviewed the claims of the predecessor applications to the extent that those claims were filed before the critical date of October 5, 2011.

1. The '381 application claims do not support the functional material limitations of the '210 application

480. The only independent originally filed claim of the '381 application recite: "An isolated oligonucleotide of between 20 to 50 nucleotides comprising a sequence consisting of SEQ ID NO: 27 or the DNA homolog thereof." (Exh. 2065.) The originally filed claims also include dependent claims that introduce limitations that the oligonucleotide comprises certain modifications.

481. A preliminary amendment was also submitted with the application that canceled the originally filed claims, and substituted new claims. The new independent claim introduced by the preliminary amendment recites: "An oligonucleotide consisting of SEQ ID NO: 27." (Exh. 2006.)

482. The originally filed and preliminarily amended claims of the '381 application contain support for the '210 application claim material limitations wherein the oligonucleotides comprise a modified nucleotide. However, those claims do not contain any support for the functional material limitations. For example, these claims do not specify that the claimed oligonucleotide be capable of binding to an exon-internal sequence and/or induce exon skipping of exon 51.

483. I note that the originally filed claims claim a nucleotide consisting of SEQ ID NO:27, which is also h51AON1. But the claims include no requirement that SEQ ID NO: 27 be

capable of binding to the same exon-internal sequence as the claimed oligonucleotide. Thus, they do not support that material limitation.

484. The claims of the ’381 application were not amended again until after the critical date of October 5, 2011. Thus, I have not considered any further amendments to the ’381 application claims.

2. The ’007 application claims do not support the functional material limitations of the ’210 application

485. The originally filed claims of the ’007 application are identical to the originally filed claims of the ’381 application. Accordingly, they also do not support the functional material limitations of the ’210 application claims.

486. The claims of the ’007 application were amended only to delete the limitation “the DNA homolog thereof” in the independent claim. (Exh. 2067.) However, the deletion of this limitation in no way supports the functional material limitations of the ’210 application claims.

487. The claims of the ’007 application were subsequently allowed after the deletion of “the DNA homolog thereof.” Thus, there are no further amendments to the ’007 application to consider.

3. The ’495 application claims do not support the functional material limitations of the ’210 application

a. Originally Filed Claims and Preliminary Amendment

488. The ’495 application was originally filed with 34 claims variously directed to methods of generating oligonucleotides (e.g., claim 1), compounds capable of hybridizing to at least two exons in a pre-mRNA (e.g., claim 16), methods of altering recognition of an exon in a

pre-mRNA (e.g., claim 22), methods of inducing exon skipping in a pre-mRNA (e.g., claim 26), and methods of altering the efficiency with which a splice donor or splice acceptor sequences is used by a splicing machinery (e.g., claim 28). (Exh. 2068.)

489. A preliminary amendment was also filed with the application. (Exh. 2069.) However, the preliminary amendment merely changed the dependency of some of the originally filed claims, and added new claims 35 – 47. New claims 35 – 47 are variously drawn to the same methods as the originally filed claims, e.g., methods of altering recognition of an exon in a pre-mRNA (e.g., claim 35), methods of inducing exon skipping in a pre-mRNA (e.g., claim 39), and methods of altering the efficiency with which a splice donor or splice acceptor sequences is used by a splicing machinery (e.g., claim 46).

490. However, it is my opinion that none of these claims support the functional material limitations of the ’210 application. In other words, none of these originally filed, or preliminary amended claims, claim an oligonucleotide capable of binding to an exon-internal sequence and inducing exon skipping, or claim that SEQ ID NO: 27 is also capable of binding to the same exon-internal sequence.

491. For example, claim 26, as preliminarily amended, recites:

> 26. A method of inducing exon skipping in a pre-mRNA, said method comprising: providing the oligonucleotide or the equivalent thereof according to claim 15; and inducing exon skipping in a pre-mRNA

(Exh. 2069.)

492. Claim 15 as preliminarily amended states:

> 15. An oligonucleotide or an equivalent thereof obtainable by a method according to claim 1.

(Exh. 2069.)

493. Claim 1 recites:

> 1. A method for generating an oligonucleotide or an equivalent thereof comprising:
>
> determining from a secondary structure of RNA from an exon, a region that assumes a structure that is hybridized to another part of said RNA (closed structure) and a region that is not hybridized in said structure (open structure); and
>
> generating said oligonucleotide or said equivalent thereof, of which at least part of said oligonucleotide or said equivalent thereof is complementary to said closed structure and of which at least another part of said oligonucleotide or said equivalent thereof is complementary to said open structure.

(Exh. 2069.)

494. As is clear, none of these claims include the functional claim limitation that the oligonucleotide is capable of binding to an exon-internal sequence, or that SEQ ID NO: 27 is also capable of binding to the same exon-internal sequence. In fact, none of the originally filed claims, or preliminarily amended claims, so much as mention an "exon-internal sequence" or SEQ ID NO: 27.

495. Claim 26 recites a method of inducing exon skipping, but does not contain a functional limitation that exon skipping is mediated by the binding of the oligonucleotide generated by claim 1 to an exon-internal sequence. Thus, claim 26 also does not support the functional limitation pertaining to exon skipping.

496. As a further example, claim 16 is directed to a compound claims, and recites:

> 16. A compound capable of hybridizing to at least two exons in a pre-mRNA encoded by a gene, said compound comprising at least two parts wherein a first part comprises an oligonucleotide having at least 8 consecutive nucleotides that are complementary to a first of said at least two exons, and wherein a second part comprises an oligonucleotide having at least 8 consecutive nucleotides that are complementary to a second of said at least two exons in said pre-mRNA.

(Exh. 2069.)

497. It is my opinion that claim 16 also does not claim the material limitations of claim 11. Consequently those claims that depend from claim 16 also do not contain the material

limitations of claim 11. For example, in addition to suffering from the same deficiencies as claim 15, the compound of claim 16 must be capable of hybridizing to at least two exons, whereas the oligonucleotide of claim 11 binds to an exon-internal sequence of exon 51. In other words, the oligonucleotide of claim 11 is capable of binding to only a single exon, and not to at least two different exons as required by the compound of claim 16. Moreover, it does not recite any of the other functional limitations that the pending claims of the '210 application require.

b. Amendment submitted on October 31, 2007

498. The '495 application claims were next substantively amended on October 31, 2007. However, the only substantive amendment was made to claim 15, and then only to incorporate the limitations of claim 1. Thus, for the reasons discussed above, claim 15 still does not recite the material limitations of claim 11 of the '210 application.

499. The October 31, 2007 amendment also added new claims. For example, new claim 51 recites:

> 51. The oligonucleotide of claim 48, comprising the sequence of h51AON1.

(Exh. 2070.)

500. New claim 48 depends from claim 15, and recites:

> 48. The oligonucleotide of claim 15, of between 14 and 50 nucleotides and comprising a DNA or RNA sequence as depicted in table 2.

(Exh. 2070.)

501. Although new claim 51 specifically recites h51AON1, it does not specify that h51AON1 is capable of binding to an exon-internal sequence of exon 51. Nor does claim 15 specify that the oligonucleotide is capable of binding to an exon-internal sequence. Accordingly,

it is my opinion that the material limitations of the '210 application claim are still not supported by the claims of the '495 application.

c. Amendment submitted on April 1, 2009

502. The only amendment was made to claim 21, which was amended to recite:

> 21. A functional equivalent of a compound ~~according to claim 16, comprising an oligonucleotide or an equivalent thereof~~ capable of hybridizing to at least two exons in a pre-mRNA encoded by a gene, said compound comprising at least two parts wherein a first part comprises an oligonucleotide having at least 8 consecutive nucleotides that are complementary to a first of said at least two exons, and wherein a second part comprises an oligonucleotide having at least 8 consecutive nucleotides that are complementary to a second of said at least two exons in said pre-mRNA, wherein the functional equivalent comprises similar hybridization characteristics in kind.

(Exh. 2071.)

503. Claim 21 was amended to include the limitations of claim 16, which as discussed above in paragraph 497, do not support the material limitations of the pending '210 application claims. Accordingly, claim 21 does not support the material limitations of the pending '210 application claims for the same reasons.

d. Amendment submitted on September 16, 2009

504. Claim 15 of the '495 application was amended to recite:

> 15. An oligonucleotide or an equivalent thereof produced by a method comprising: determining from a secondary structure of RNA from an exon, ~~a region that assumes~~ regions that assume a structure that is hybridized to another part of the RNA (closed structure) and ~~a region that is~~ regions that are not hybridized in the structure (open structure); ~~and~~ selecting, from the determined regions of closed structure and open structure, a region of closed structure and a region of open structure; and generating the oligonucleotide or the equivalent thereof, of which at least part of the oligonucleotide or equivalent thereof is complementary to the selected region of closed structure and of which at least another part of the oligonucleotide or equivalent thereof is complementary to the selected region of open structure.

(Exh. 2072.)

505. The amendments to claim 15 merely further refine the "region" selection process that was then being claimed. Accordingly, these amendments also fail to disclose the material limitations of the pending '210 application claims.

506. The amendment submitted on September 16, 2009 also added new claims 54 – 69. New claims 54-56 are product-by-process claims that claim a compound produced by determining the secondary structure of the RNA of a single exon. The differences in these claims reflect different regions (non-contiguous regions, or portions of splice donor or splice accept sites) to which the produced compound is complementary. The language of these claims largely tracks the limitations of claim 15, and also does not convey the material limitations "capable of binding to an exon-internal site of exon 51" and "inducing exon skipping."

507. New claims 64 is ultimately dependent on claim 15, and recites:

> 64. The oligonucleotide or equivalent thereof of claim 63, wherein the exon comprises an exon selected from the group consisting of human exons 2, 8, 9, 17, 19, 29, 40 – 46, 48 – 53, 55 and 59.

(Exh. 2072.)

508. New claim 63 recites:

> 63. The oligonucleotide or equivalent thereof of claim 61, wherein the gene from which the RNA comprising said exon is transcribed, encodes an aberrant Duchenne muscular dystrophy gene.

(Exh. 2072.)

509. New claim 61 recites:

> 61. The oligonucleotide or equivalent thereof of claim 15, wherein a pre-mRNA comprising the exon exhibits undesired splicing in a subject.

(Exh. 2072.)

510. It is my opinion that these claims also fail to recite the material limitations of the '210 application claims. Although new claim 64 recites various exons, including exon 51, that

may be used to produce the oligonucleotide of claim 15, new claim 64 fails to include the material limitation that the oligonucleotide is "capable of binding to an exon-internal site of exon 51" and "inducing exon skipping of exon 51."

511. New claim 67 recites:

> 67. The oligonucleotide or equivalent thereof of claim 15, wherein the oligonucleotide or equivalent thereof does not overlap a splice donor and/or a splice acceptor sequence of said exon.

(Exh. 2072.)

512. New claim 67 merely adds the limitation that the oligonucleotide of claim 15 does not overlap a splice donor and/or a splice acceptor sequence of the exon. However, in my opinion, this limitation does not convey the material limitation that the oligonucleotide is capable of binding to an "exon-internal site." Nor does it convey the limitation that the binding of an oligonucleotide is capable of inducing exon skipping of exon 51.

513. As discussed above in paragraphs 443-445, it is not clear what is intended by the phrase "exon-internal sequence." Although the specification of the '495 application suggests that an exon-internal sequence is somehow different from a splice site (See e.g., Exh. 2041 at [0015]), it is my opinion that merely stating that the oligonucleotide of the claim does not bind to a splice site is not sufficient to convey the functional limitation that the oligonucleotide is capable of binding to an exon-internal site, and, by so binding, induce exon skipping. Accordingly, the new claims added September 16, 2009 also do not support the material limitations of the '210 application.

e. Amendment submitted June 24, 2010

514. Claim 15 was again amended on June 24, 2010, to recite:

> 15. An oligonucleotide or an equivalent thereof produced by a method comprising: (a) determining from a secondary structure of a pre-m RNA from an exon, ~~a~~ regions that assume a structure that is hybridized to ~~another~~ part of ~~the~~

said pre-mRNA (closed structure) and regions that are not hybridized in the structure (open structure), wherein the gene from which said pre-mRNA comprising said exon is transcribed is an aberrant Duchenne muscular dystrophy (DMD) gene; (b) designing an oligonucleotide or equivalent thereof comprising said structure of (a) of which at least a part is complementary to a closed structure and of which at least another part is complementary to an open structure, wherein binding of said oligonucleotide or the equivalent thereof comprising said structure to said pre-mRNA alters the splicing of said pre-mRNA, and wherein said designing is based on the results of said determining step; ~~selecting, from the determined regions of closed structure and open structure, a region of closed structure and a region of open structure~~; (c) and generating the oligonucleotide or the equivalent thereof of step (b)~~, of which at least part of the oligonucleotide or equivalent thereof is complementary to the selected region of closed structure and of which at least another part of the oligonucleotide or equivalent thereof is complementary to the selected region of open structure~~.

(Exh. 2073.)

515. Claim 15 was amended to specify that the binding of the oligonucleotide alters the splicing of the pre-mRNA. It is my opinion that including the limitation that the claimed oligonucleotide alters the splicing of the pre-mRNA does not convey that the oligonucleotide functionally binds to an exon-internal sequence, and as a result of that binding induces exon skipping of exon 51.

516. The term exon skipping carries a very specific meaning to those of ordinary skill in the art. In my opinion, mere recitation that the binding of the oligonucleotide "alters splicing" is not sufficiently specific to convey that the binding of the oligonucleotide induces exon skipping. Accordingly, amended claim 15 does not provide support for the material limitations of the pending '210 application claims.

f. Amendment submitted March 14, 2011

517. Claim 15 was again amended on March 14, 2011 to recite:

15. An oligonucleotide or an equivalent thereof produced by a method comprising: (a) determining from a secondary structure of a pre-m RNA from an exon, ~~a~~ regions that assume a structure that is hybridized to part of said pre-mRNA (closed structure) and regions that are not hybridized in the structure (open structure), wherein the gene from which said pre-mRNA comprising said

> exon is transcribed is an aberrant Duchenne muscular dystrophy (DMD) gene, wherein said exon comprises an exon selected from the group consisting of human exons 2, 8, 9, 17, 19, 29, 40, 41, 42, 43, 44, 45, 46, 49, 50, 51, 52, 53, 55, and 59; (b) designing an oligonucleotide or equivalent thereof comprising said structure of (a) of which at least a part is complementary to a closed structure and of which at least another part is complementary to an open structure, wherein binding of said oligonucleotide or the equivalent thereof comprising said structure to said pre-mRNA alters the splicing of said pre-mRNA, and wherein said designing is based on the results of said determining step; (c) and generating the oligonucleotide or the equivalent thereof of step (b).

(Exh. 2074.)

518. The amendment to claim 15 essentially adds the limitation of claim 64. However, the amended claim still fails to include the material limitation that the oligonucleotide is "capable of binding to an exon-internal site of exon 51" and "inducing exon skipping of exon 51."

519. The March 14, 2011 amendments also added new claims 70 – 75. The essential difference between new claims 70 - 75, and those that have already been discussed, is that these claims incorporate specific oligonucleotide sequences. However, those oligonucleotide sequences have already been claimed in prior iterations. Importantly, the new claim amendments fail to specify that h51AON1 is capable of binding to the same exon-internal sequence as the oligonucleotide that is claimed. Accordingly, there is no new support for the material limitations of the '210 application claims in these new claims.

520. The claims of the ''495 application were not substantively amended again until after the critical date of October 5, 2011. I have not considered any of the claim amendments made after that date since they are irrelevant to the determination of whether the material limitations were present in the claims prior to the one year deadline.

XI. CONCLUSIONS

521. In summary, in view of the materials I have considered, and for the reasons I have explained in this declaration, in my opinion:

- the ’495 application does not provide a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the ’495 application that the AZL applicants had possession of the full scope of claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103;
- the ’495 application does not provide sufficient information to permit a person of ordinary skill in the art as of the application’s filing date to practice the full scope of claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103 without undue experimentation;
- the ’210 application does not provide a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the ’210 application that the AZL applicants had possession of the full scope of claims 11, 12, 14, 15, and 17-29;
- the ’210 application does not provide sufficient information to permit a person of ordinary skill in the art as of the application’s filing date to practice the full scope of claims 11, 12, 14, 15, and 17-29 without undue experimentation;
- the ’992 application does not provide a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the ’992 application that the AZL applicants had possession of the full scope of claims 1-7 and 10-27;
- the ’992 application does not provide sufficient information to permit a person of ordinary skill in the art as of the application’s filing date to

practice the full scope of claims 1-7 and 10-27 without undue experimentation;

- the ’279 application does not provide a written description that would reasonably convey to a person of ordinary skill in the art as of the filing date of the ’279 application that the AZL applicants had possession of the full scope of claims 1-16 and 20-26;
- the ’279 application does not provide sufficient information to permit a person of ordinary skill in the art as of the application’s filing date to practice the full scope of claims 1-16 and 20-26 without undue experimentation;
- the claims of the ’495, ’210, ’992, and ’279 applications, when read in the context of the AZL applications and the record of the examination of the patent application by the Patent Office, do not inform those of ordinary skill in the art with reasonable certainty about the scope of the invention recited in the claims; and
- the material limitations of the ’210 application claims were not included in any claim presented in the ’381, ’007, or ’495 applications before October 5, 2011.

XII. COMPENSATION

522. For my work as an expert consultant in these interferences, I am being compensated at a rate of £350 per hour (£600 per hour when testifying), plus reimbursement for related out-of-pocket expenditures.

523. I understand that the real parties in interest are Academish Ziekenhuis Leiden and its licensee Prosensa Therapeutics, and the University of Western Australia and its licensee Sarepta Therapeutics. I do not have any financial interest in any of these parties or in the outcome of this proceeding.

524. I believe that I can provide an independent opinion in this matter as an independent expert witness.

XIII. PRIOR EXPERT TESTIMONY

525. I have not provided expert testimony in any proceeding as of the date I signed this declaration.

526. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

527. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I also declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

_____ _____

Date Matthew J. A. Wood, M.D., D. Phil.

523. I understand that the real parties in interest are Academish Ziekenhuis Leiden and its licensee Prosensa Therapeutics, and the University of Western Australia and its licensee Sarepta Therapeutics. I do not have any financial interest in any of these parties or in the outcome of this proceeding.

524. I believe that I can provide an independent opinion in this matter as an independent expert witness.

XIII. PRIOR EXPERT TESTIMONY

525. I have not provided expert testimony in any proceeding as of the date I signed this declaration.

526. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

527. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I also declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

11/18/2014
Date

Matthew J. A. Wood, M.D., D. Phil.

APPENDIX A
List of Materials Considered

2003: CV of Matthew J.A. Wood

2004: S. J. Errington *et al*., "Target selection for antisense oligonucleotide induced exon skipping in the dystrophin gene." J. Gene Med., 5(6): 518-527 (2003).

2005: A. G. Douglas *et al*., "Splicing therapy for neuromuscular disease." M. Cell. Neurosc., 56: 169-185 (2013).

2006: D. A. Braasch *et al*., "Novel antisense and peptide nucleic acid strategies for controlling gene expression." Biochemistry, 41(14): 4503-4510 (2002).

2007: A. A. Koshkin *et al*., "LNA (Locked Nucleic Acids): Synthesis of the adenine, cytosine, guanine, 5-methylcytosine, thymine and uracil bicyclonucleoside monomers, oligomerisation, and unprecedented nucleic acid recognition." Tetrahedron, 54(14): 3607-3630 (1998).

2008: J. Summerton *et al*., "Morpholino antisense oligomers: design, preparation, and properties." Antisense Nucleic Acid Drug Dev., 7(3): 187-195 (1997).

2009: D. A. Braasch *et al*., "Locked nucleic acid (LNA): fine-tuning the recognition of DNA and RNA." Chem. Biol., 8(1): 1-7 (2001).

2010: A. Aartsma-Rus *et al*., "Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy." Neuromuscul. Disord., 12: S71-S77 (2002).

2011: S. M. Hammond *et al.*, "Correlating *In Vitro* Splice Switching Activity With Systemic *In Vivo* Delivery Using Novel ZEN-modified Oligonucleotides" Mol. Ther.-Nucleic Acids, 2014 (*in press*).

2012: J. C. Van Deutekom *et al*., "Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells." Hum. Mol. Genet., 10(15): 1547-1554 (2001).

2013: V. Arechavala-Gomeza *et al*., "Comparative analysis of antisense oligonucleotide sequences for targeted skipping of exon 51 during dystrophin pre-mRNA splicing in human muscle." Hum. Gene Ther., 18(9): 798-810 (2007).

2014: A. Aartsma-Rus *et al*., "Guidelines for antisense oligonucleotide design and insight into splice-modulating mechanisms." Mol. Ther., 17(3): 548-553 (2009).

2015: B. Wu *et al.*, "Targeted skipping of human dystrophin exons in transgenic mouse model systemically for antisense drug development." *PloS one*, 6(5): e19906 (2011).

2016: A. Aartsma-Rus *et al*., "Functional analysis of 114 exon-internal AONs for targeted DMD exon skipping: indication for steric hindrance of SR protein binding sites." Oligonucleotides, 15(4): 284-197 (2005).

2017: C. J. Mann *et al*., "Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy." J. Gene Med., 4(6): 644-654 (2002).

2018: A. Aartsma-Rus *et al*., "Therapeutic antisense-induced exon skipping in cultured muscle cells from six different DMD patients." Hum. Mol. Genet., 12(8): 907-914 (2003).

2019: C. T. Fragall *et al*., "Mismatched single stranded antisense oligonucleotides can induce efficient dystrophin splice switching." BMC Med. Genet., 12(1): 141 (2011).

2020: H. A. Heemskerk *et al*., "In vivo comparison of 2′-O-methyl phosphorothioate and morpholino antisense oligonucleotides for Duchenne muscular dystrophy exon skipping." J. Gene Med., 11(3): 257-266 (2009).

2021: Isis Pharmaceuticals Website: <http://www.isispharm.com/Pipeline/Therapeutic-Areas/Other.htm>

2022: C. A. Stein, “Delivery of antisense oligonucleotides to cells: a consideration of some of the barriers.” Chemistry Today, 32: 4-7 (2014).

2023: C. J. Mann *et al*., "Antisense-induced exon skipping and synthesis of dystrophin in the mdx mouse." Proc. Natl. Acad. Sci., 98(1): 42-47 (2001).

2024: M. Bremmer-Bout *et al*., "Targeted exon skipping in transgenic hDMD mice: A model for direct preclinical screening of human-specific antisense oligonucleotides." Mol. Ther. 10(2): 232-240 (2004).

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2028: K. Anthony *et al.*, “Dystrophin quantification, Biological and translations research implications,” Neurology, 83:1-8 (2014) (on-line preprint).

2029: X. Tian et al., "Imaging oncogene expression." Ann. N. Y. Acad. Sci., 1002(1): 165-188 (2003).

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2031: L. J. Popplewell *et al*., "Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human *DMD* gene: Implications for future clinical trials." Neuromuscul. Disord., 20(2): 102-110 (2010).

2032: E. Kaye, "Results of the Eteplirsen Phase 2b and Phase 2b Extension Study in Duchenne Muscular Dystrophy." Abstract for 8th Annual Meeting of the Oligonucleotide Therapeutics Society (2012).

2033: S. Cirak *et al*., "Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study." Lancet, 378(9791): 595-605 (2011).

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2036: N. M. Goemans *et al*., "Systemic administration of PRO051 in Duchenne's muscular dystrophy." N. Engl. J. Med., 364(16): 1513-1522 (2011).

2037: T. Voit *et al*., "Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study." Lancet Neurol., 13(10): 987-96 (2014).

2038: K. M. Flanigan *et al*., "Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial." Neuromuscul. Disord., 24(1): 16-24 (2014).

2039: Prosensa Press Release dated September 20, 2013

2040: GlaxoSmithKline Press Release dated January 13, 2014.

2041: U.S. Patent Application Publication US 2006/0147952

2042: International Patent Application No. PCT/NL2003/000214

2043: U.S. Patent Application Publication US 2013/0072671

2044: Updated Filing Receipt mailed December 11, 2012, In U.S. Application no. 13/550,210

2045: Academish Ziekenhuis Leiden Clean Copy of Claims and Sequences submitted August 5, 2014, in Interference No. 106,007 (RES)

2046: U.S. Patent No. 8,455,636

2047: Academish Ziekenhuis Leiden Clean Copy of Claims and Sequences submitted August 5, 2014, in Interference No. 106,008 (RES)

2048: U.S. Patent No. 7,807,816

2049: U.S. Patent No. 7,960,541

2050: Academish Ziekenhuis Leiden Clean Copy of Claims and Sequences submitted October 15, 2014, in Interference No. 106,013 (RES)

2051: U.S. Patent No. 8,486,907

2052: U.S. Patent Application Publication US 2014/0275212

2053: Amendment Under 37 CFR §1.312- Notice of Allowance Mailed, dated September 19, 2014, submitted in U.S. Application No. 14/248,279

2054: Excerpts from the prosecution history of U.S. Application No. 11/233,495

2055: Excerpts from the prosecution history of U.S. Application No. 13/550,210

2056: Excerpts from the prosecution history of U.S. Application No. 14/198,992

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2063: Response & Amendments filed on January 21, 2014, in U.S. Patent Application No. 13/550,210.

2064: Response & Amendments filed on May 12, 2014, in U.S. Patent Application No. 13/550,210.

2065: Claims from Application filed on December 22, 2010, in U.S. Patent Application No. 12/976,381.

2067: Preliminary Amendment filed on November 7, 2008, in U.S. Patent Application No. 12/198,007.

2068: Claims from Application filed on September 21, 2005, in U.S. Patent Application No. 11/233,495.

2069: Preliminary Amendment filed on September 21, 2005, in U.S. Patent Application No. 11/233,495.

2070: Amendment filed on October 31, 2007, in U.S. Patent Application No. 11/233,495.

2071: Amendment filed on April 1, 2009, in U.S. Patent Application No. 11/233,495.

2072: Amendment filed on September 16, 2009, in U.S. Patent Application No. 11/233,495.

2073: Amendment After Non-Final Action filed on June 24, 2010, in U.S. Patent Application No. 11/233,495.

2074: Amendment In Response to Advisory Action filed on March 14, 2011, in U.S. Patent Application No. 11/233,495.

2076: Applicant -Initiated Interview Summary and Notice of Allowance filed on May 19, 2014, in U.S. Patent Application No. 13/550,210.

2082: Sarepta Therapeutics Press Release dated August 15, 2011.

2083: Kinali *et al.*, Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study, Lancet Neurology, 8:918-928 (Oct. 2009).

APPENDIX B

Filed on behalf of: Senior Party Academisch Ziekenhuis Leiden
By: Timothy M. Murphy, Esq.
Kathleen M. Williams, Esq.
Elizabeth N. Spar, Esq.
Brandon T. Scruggs, Esq.
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004

Paper No. ___

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent No. 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)

v.

Academisch Ziekenhuis Leiden,
Senior Party
(Application No. 11/233,495,
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina Theodora van Deutekom, Johannes Theodorus den Dunnen and Annemieke Aartsma-Rus).

Patent Interference No. 106,007 (RES)
(Technology Center 1670)

ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES

UWA EXHIBIT 2045
University of Western Australia
v.
Academisch Ziekenhuis Leiden
Interference Nos. 106,007, 106,008 & 106,013

ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES

Claims:

Claim 15. An isolated antisense oligonucleotide of 15 to 80 nucleotides comprising at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-, phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

Claim 76. An isolated antisense oligonucleotide of 18 to 80 nucleotides comprising at least the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre- mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic acid.

Claim 77. The oligonucleotide of claim 15, wherein the oligonucleotide is 18 nucleotides and comprises the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA.

Claim 78. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a

phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

Claim 79. The oligonucleotide of claim 78, wherein said exon-internal sequence comprises a consecutive part of between 16 and 50 nucleotides of said exon and said oligonucleotide is complementary to said consecutive part.

Claim 80. The oligonucleotide of claim 15, wherein the oligonucleotide is complementary to exon 53 of the human dystrophin pre-mRNA.

Claim 82. The oligonucleotide of claim 15 or 100, wherein said modification consists of a 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate.

Claim 84. The oligonucleotide of claim 15, 78, or 100, wherein the oligonucleotide comprises a modification, said modification comprising a morpholine ring and a phosphorodiamidate linkage.

Claim 86. The oligonucleotide of claim 84, which is a morpholine phosphorodiamidate oligonucleotide.

Claim 88. The oligonucleotide of claim 15, 78, or 100, wherein the oligonucleotide induces exon 53 skipping of the human dystrophin pre-mRNA and dystrophin expression at the muscle cell upon transfection of primary human muscle cells with at least 100 nM of said oligonucleotide and incubation for at least 16 hours.

Claim 89. The antisense oligonucleotide of claim 88, wherein exon 53 skipping is detected by RT-PCR and/or sequence analysis.

Claim 90. The oligonucleotide of claim 88, wherein dystrophin expression at the muscle cell is detected by immunohistochemical and/or western blot analysis.

Claim 97. The oligonucleotide of claim 78 or 100, wherein the bases of said nucleotides of said oligonucleotide consist of DNA bases or consists of RNA bases.

Claim 98. The oligonucleotide of claim 15, 76, 77, 78, or 100, said oligonucleotide consisting of RNA.

Claim 100. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and is capable of inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

Claim 101. The oligonucleotide of claim 15, 76, 77, 78, 97 or 100, said oligonucleotide being less than 50 nucleotides in length.

Claim 102. The oligonucleotide of claim 15, 76, or 77, said oligonucleotide being less than 80 nucleotides in length.

Claim 103. The oligonucleotide of claim 78 or 100, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence.

Biotechnology Sequences:

SEQ ID NO: 29 = cuguugccuc cgguucug

July 31, 2014

Respectfully Submitted,

/Timothy M. Murphy/

Timothy M. Murphy
Reg. No. 33,198
Lead Attorney for Senior Party Academisch Ziekenhuis Leiden
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004
TMurphy@sunsteinlaw.com

CERTIFICATE OF SERVICE

Pursuant to S.O. ¶ 105, I hereby certify that the Junior Party University of Western Australia has been duly served with a copy of the foregoing and a copy of this Certificate of Service. The Junior Party University of Western Australia has been served per S.O. ¶ 105.3. Specifically, the Junior Party University of Western Australia was served after 5:00 pm Eastern Time on July 31, 2014 but before 12:00 am Eastern Time on August 1, 2014 by posting to the Interference Web Portal.

/Timothy M. Murphy/

Timothy M. Murphy
Reg. No. 33,198
Lead Attorney for Senior Party Academisch Ziekenhuis Leiden
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004
TMurphy@sunsteinlaw.com

APPENDIX C

Filed on behalf of: Senior Party Academisch Ziekenhuis Leiden
By: Timothy M. Murphy, Esq.
Kathleen M. Williams, Esq.
Elizabeth N. Spar, Esq.
Brandon T. Scruggs, Esq.
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004

Paper No. ___

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patents 7,960,541 and 7,807,816
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)

v.

Academisch Ziekenhuis Leiden,
Senior Party
(Application13/550,210,
Inventor: Judith C. van Deutekom).

Patent Interference No. 106,008 (RES)
(Technology Center 1670)

ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES

ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES

Claims:

Claim 11. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a morpholine ring, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

Claim 12. The oligonucleotide of claim 11, 15, 19, or 26, said exon-internal sequence comprising a consecutive part of between 16 and 50 nucleotides of said exon and wherein said oligonucleotide is complementary to said consecutive part.

Claim 14. The oligonucleotide of claim 11, wherein said oligonucleotide further comprises a phosphorodiamidate internucleoside linkage.

Claim 15. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a peptide nucleic acid and/or locked nucleic acid, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

Claim 17. The oligonucleotide of claim 15, wherein each linkage is a phosphorodiamidate internucleoside linkage.

Claim 18. The oligonucleotide of claim 11 or 17, wherein the oligonucleotide is a morpholino phosphorodiamidate oligonucleotide.

Claim 19. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a 2'-*O*-methyl ribose moiety, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping

of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

Claim 20. The oligonucleotide of claim 19, further comprising a phosphorothioate internucleoside linkage.

Claim 21. The oligonucleotide of claim 19 wherein each internucleoside linkage is a phosphorothioate linkage.

Claim 22. The oligonucleotide of claim 19, wherein said oligonucleotide is a 2'-O-methyl phosphorothioate oligonucleotide.

Claim 23. The oligonucleotide of claim 11, 15 or 19, wherein the oligonucleotide induces exon 51 skipping in the human dystrophin pre-mRNA and dystrophin expression in the muscle cell upon transfection of human muscle cells with at least 100 nM of said oligonucleotide and incubation for at least 16 hours.

Claim 24. The antisense oligonucleotide of claim 23, wherein exon 51 skipping is detected by RT-PCR and/or sequence analysis.

Claim 25. The oligonucleotide of claim 23, wherein dystrophin expression in the muscle cell is detected by immunohistochemical and/or western blot analysis.

Claim 26. An isolated antisense oligonucleotide of 20 to 50 nucleotides in length, comprising a modification which confers increased resistance to RNAseH, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

Claim 27. The oligonucleotide of claim 11, 15, 19 or 26 wherein the bases of said nucleotides of said oligonucleotide consist of DNA bases or RNA bases.

Claim 28. The oligonucleotide of claim 11, 15, 19 or 26, said oligonucleotide being less than 50 nucleotides in length.

Claim 29. The oligonucleotide of claim 11, 15, 19 or 26, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence.

Biotechnology Sequences:

SEQ ID NO: 27 = UCAAGGAAGAUGGCAUUUCU

August 5, 2014

Respectfully Submitted,

/Brandon T. Scruggs/

Brandon T. Scruggs
Reg. No. 57,692
Backup Attorney for Senior Party Academisch Ziekenhuis Leiden
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004
BScruggs@sunsteinlaw.com

CERTIFICATE OF SERVICE

Pursuant to S.O. ¶ 105, I hereby certify that the Junior Party University of Western Australia has been duly served with a copy of the foregoing and a copy of this Certificate of Service. The Junior Party University of Western Australia has been served per S.O. ¶ 105.3. Specifically, the Junior Party University of Western Australia was served on August 5, 2014 before 5:00 pm Eastern Time by posting to the Interference Web Portal.

/Brandon T. Scruggs/

Brandon T. Scruggs
Reg. No. 57,692
Backup Attorney for Senior Party Academisch Ziekenhuis Leiden
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004
BScruggs@sunsteinlaw.com

03909/05005 2148859.1

APPENDIX D

Filed on behalf of: Senior Party Academisch Ziekenhuis Leiden
By: Timothy M. Murphy, Esq.
Kathleen M. Williams, Esq.
Elizabeth N. Spar, Esq.
Brandon T. Scruggs, Esq.
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004

Paper No. ___

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent No. 8,486,907,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)

v.

Academisch Ziekenhuis Leiden,
Senior Party
(Application No. 14/198,992,
Inventor: Judith Christina Theodora van Deutekom).

Patent Interference No. 106,013 (RES)
(Technology Center 1600)

ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES

UWA EXHIBIT 2050
University of Western Australia
v.
Academisch Ziekenhuis Leiden
Interference Nos. 106,007, 106,008 & 106,013

ACADEMISH ZIEKENHUIS LEIDEN CLEAN COPY OF CLAIMS AND SEQUENCES

Claims:

Claim 1. A method for inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 20 to 50 nucleotides in length to a cell, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

Claim 2. A method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a patient by inducing the skipping of exon 51 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 20 to 50 nucleotides in length to a cell of said patient, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 51 of the human dystrophin pre-mRNA and inducing skipping of exon 51, wherein h51AON1 (UCAAGGAAGAUGGCAUUUCU) (SEQ ID NO: 27) is capable of binding to said exon-internal sequence.

Claim 3. The method of claim 1, wherein the cell is a muscle cell.

Claim 4. The method of claim 1, wherein the cell is from a subject with Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD).

Claim 5. The method of claim 1, wherein mRNA produced from skipping of exon 51 of the dystrophin pre-mRNA encodes a functional dystrophin protein or a dystrophin protein of a Becker Muscular Dystrophy patient.

Claim 6. The method of claim 1, wherein the oligonucleotide comprises DNA.

Claim 7. The method of claim 1, wherein the oligonucleotide comprises RNA.

Claim 10. The method of claim 1, wherein the oligonucleotide comprises a modification.

Claim 11. The method of claim 10, wherein the modification is selected from the group consisting of: a morpholine ring, a 2'-*O*-methyl ribose moiety, a phosphorothioate internucleoside linkage, a phosphorodiamidate internucleoside linkage, a peptide nucleic acid, and a locked nucleic acid.

Claim 12. The method of claim 11, wherein the oligonucleotide comprises a phosphorothioate internucleoside linkage.

Claim 13. The method of claim 12, wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

Claim 14. The method of claim 13, wherein the oligonucleotide is a 2'-*O*-methyl phosphorothioate oligoribonucleotide.

Claim 15. The method of claim 11, wherein the modification is selected from the group consisting of a 2'-*O*-methyl ribose moiety, a phosphorothioate internucleoside linkage and a locked nucleic acid.

Claim 16. The method of claim 11, wherein the oligonucleotide comprises a phosphorodiamidate internucleoside linkage.

Claim 17. The method of claim 16, wherein each internucleoside linkage of the oligonucleotide is a phosphorodiamidate internucleoside linkage.

Claim 18. The method of claim 17, wherein the oligonucleotide is a morpholino phosphorodiamidate oligonucleotide.

Claim 19. The method of claim 1, wherein the oligonucleotide induces exon 51 skipping in the human dystrophin pre-mRNA and dystrophin expression in a muscle cell upon transfection of human muscle cells with at least 100 nM of said oligonucleotide and incubation for at least 16 hours.

Claim 20. The method of claim 1, wherein exon 51 skipping is detected by RT-PCR and/or sequence analysis.

Claim 21. The method of claim 19, wherein dystrophin expression in a muscle cell is detected by immunohistochemical and/or western blot analysis.

Claim 22. The method of claim 1, said exon internal sequence comprising a consecutive part of between 16 and 50 nucleotides of said exon and wherein said oligonucleotide is complementary to said consecutive part.

Claim 23. The method of claim 1, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence.

Claim 24. The method of claim 1, wherein the bases of said oligonucleotide consist of DNA bases or RNA bases.

Claim 25. The method of claim 1, said oligonucleotide being less than 50 nucleotides in length.

Claim 26. The method of claim 1, said oligonucleotide comprising a modification which confers increased resistance to an endonuclease.

Claim 27. The method of claim 26, wherein said endonuclease is RNAase H.

Biotechnology Sequences:

SEQ ID NO: 27 = UCAAGGAAGAUGGCAUUUCU

October 15, 2014

Respectfully Submitted,

/Timothy M. Murphy/

Timothy M. Murphy
Reg. No. 33,198
Lead Attorney for Senior Party Academisch Ziekenhuis Leiden
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004
TMurphy@sunsteinlaw.com

CERTIFICATE OF SERVICE

Pursuant to S.O. ¶ 105, I hereby certify that the Junior Party University of Western Australia has been duly served with a copy of the foregoing and a copy of this Certificate of Service. The Junior Party University of Western Australia has been served per S.O. ¶ 105.3. Specifically, the Junior Party University of Western Australia was served before 5:00 pm Eastern Time on October 15, 2014 by posting to the Interference Web Portal.

/Timothy M. Murphy/

Timothy M. Murphy
Reg. No. 33,198
Lead Attorney for Senior Party Academisch Ziekenhuis Leiden
Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, MA 02110
Tel: 617-443-9292
Fax: 617-443-0004
TMurphy@sunsteinlaw.com

APPENDIX E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	van Deutekom et al.	Docket No.:	3909/1033
Appl. No:	14/248,279	Art Unit:	1674
Filed:	08-Apr-2014	Examiner:	Chong, Kimberly
		Conf. No:	7120

Title: MODULATION OF EXON RECOGNITION IN PRE-MRNA BY INTERFERING WITH THE SECONDARY RNA STRUCTURE

VIA USPTO ELECTRONIC FILING SYSTEM

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 CFR §1.312- NOTICE OF ALLOWANCE MAILED

Dear Sir:

Please amend the above-identified application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Please enter the following amendment and remarks.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Previously Presented) A method for inducing the skipping of exon 53 of the human dystrophin pre-mRNA in a subject with Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD), or a cell derived from the subject, said method comprising providing an oligonucleotide of 15 to 50 nucleotides in length to said subject or said cell, wherein said oligonucleotide sequence is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, wherein said oligonucleotide induces skipping of said exon in the subject or the cell and wherein mRNA produced from skipping exon 53 of the dystrophin pre-mRNA encodes a functional dystrophin protein or a dystrophin protein of a Becker subject.

2. (Previously Presented) A method for treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in a subject by inducing the skipping of exon 53 of the human dystrophin pre-mRNA, said method comprising providing an oligonucleotide of 15 to 50 nucleotides in length, said oligonucleotide sequence is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and, wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, and wherein said oligonucleotide induces skipping of said exon in the subject.

3. (Original) The method of claim 1, wherein the cell is a muscle cell.

4. (Original) The method of claim 1, wherein the oligonucleotide comprises a modification.

5. (Original) The method of claim 4, wherein the modification is selected from the group consisting of: a morpholine ring, a 2'-*O*-methyl ribose moiety, a phosphorothioate internucleoside linkage, a phosphorodiamidate internucleoside linkage, a peptide nucleic acid, and a locked nucleic acid.

6. (Original) The method of claim 5, wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

7. (Original) The method of claim 6, wherein the oligonucleotide is a 2'-*O*-methyl phosphorothioate oligonucleotide.

8. (Original) The method of claim 5, wherein the oligonucleotide comprises a phosphorodiamidate internucleoside linkage.

9. (Original) The method of claim 8, wherein each internucleoside linkage of the oligonucleotide is a phosphorodiamidate internucleoside linkage.

10. (Original) The method of claim 9, wherein the oligonucleotide is a morpholino phosphorodiamidate oligonucleotide.

11. (Original) The method of claim 1, wherein the bases of said oligonucleotide consist of DNA bases or RNA bases.

12. (Previously Presented) The method of claim 1, wherein the oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA and dystrophin expression in the muscle cell upon transfection of human muscle cells with at least 100 nM of said oligonucleotide and incubation for at least 16 hours.

13. (Previously Presented) The method of claim 12, wherein exon 53 skipping is detected by RT-PCR and/or sequence analysis.

14. (Previously Presented) The method of claim 12, wherein dystrophin expression in the muscle cell is detected by immunohistochemical and/or western blot analysis.

15. (Previously Presented) The method of claim 1, wherein said oligonucleotide is less than 50 nucleotides.

16. (Previously Presented) The method of claim 2, wherein said oligonucleotide is less than 50 nucleotides.

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (Previously Presented) An expression vector encoding a transcript comprising an oligonucleotide, wherein the oligonucleotide is 15 to 50 nucleotides in length, wherein said oligonucleotide sequence is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA.

21. (Original) A gene delivery vehicle comprising the expression vector of claim 20, wherein the vehicle is a viral vector.

22. (Previously Presented) The method of claim 1, wherein said oligonucleotide is 18 nucleotides and comprises the base sequence of the sequence CUGUUGCCUCCGGUUCUG) (SEQ ID NO: 29).

23. (Previously Presented) The method of claim 1, wherein said exon-internal sequence comprises a consecutive part of between 16 and 50 nucleotides of said exon and said oligonucleotide is complementary to said consecutive part.

24. (Previously Presented) The method of claim 1, wherein the bases of said nucleotides of said oligonucleotide consist of DNA bases or consist of RNA bases.

25. (Previously Presented) The method of claim 1, said oligonucleotide consisting of RNA.

26. (Previously Presented) The method of claim 1, wherein said oligonucleotide is capable of binding without mismatches to said exon-internal sequence.

REMARKS

A Notice of Allowance was mailed on August 19, 2014 allowing pending claims 1-26. Applicants hereby cancel claims 17-19 without prejudice. No new matter has been entered and Applicant believes no new issues have been raised.

Applicants reserve the right to pursue the subject matter of any canceled claims as originally filed in this or one or more subsequent patent applications.

The Applicants request that the examiner contact the undersigned if it will assist further examination of this application.

Applicants do not believe any extension of time is required for timely consideration of this response. In the event that an extension has been overlooked, this conditional petition of extension is hereby submitted. Applicant requests that deposit account number 19-4972 be charged for any fees that may be required for the timely consideration of this application.

Date: September 19, 2014

Respectfully submitted,

/Kathleen M. Williams, #34,380/

Kathleen M. Williams, Ph.D.
Registration No. 34,380
Attorney for Applicant

Sunstein Kann Murphy & Timbers LLP
125 Summer Street
Boston, Massachusetts 02110-1618
Tel: (617) 443-9292
Fax: (617) 443-0004

03909/01033 2174159.1